

# Exhibit T

Brooke T. Mossman, M.S., Ph.D.

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IN THE UNITED STATES DISTRICT COURT  
FOR THE EASTERN DISTRICT OF NEW JERSEY

- - -

IN RE: JOHNSON & :  
JOHNSON TALCUM POWDER :  
PRODUCTS MARKETING, :  
SALES PRACTICES, AND : NO. 16-2738  
PRODUCTS LIABILITY : (FLW) (LHG)  
LITIGATION :  
:  
THIS DOCUMENT RELATES :  
TO ALL CASES :

- - -

April 8, 2019

- - -

Videotaped deposition of  
BROOKE T. MOSSMAN, M.S., Ph.D., taken  
pursuant to notice, was held at Hotel  
Vermont, 41 Cherry Street, Burlington,  
Vermont, beginning at 9:12 a.m., on the  
above date, before Michelle L. Gray, a  
Registered Professional Reporter,  
Certified Shorthand Reporter, Certified  
Realtime Reporter, and Notary Public.

- - -

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Brooke T. Mossman, M.S., Ph.D.

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I N D E X

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Testimony of:  
BROOKE T. MOSSMAN, M.S., Ph.D.

By Mr. Smith 14

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3	- - -			3	now on the record. My name is Dan		
4				4	Lawlor. I'm a videographer with		
5	NO. DESCRIPTION PAGE			5	Golkow Litigation Services.		
6	Mossman-46 Impact Factor Of Journal of Toxicology Web Printout	492		6	Today's date is April 8th, 2019.		
7				7	And the time is 9:12 a.m.		
8				8	This video deposition is		
9	Mossman-47 Cancer Epidemiology Biomarkers & Prevention (Karageorgi)	501		9	being held in Burlington, Vermont,		
10				10	in the matter of talcum powder		
11				11	litigation, MDL Number 2738.		
12				12	Counsel will be noted on the		
13				13	stenographic record.		
14				14	The deponent today is Brooke		
15				15	Mossman, Ph.D.		
16				16	The court reporter is		
17				17	Michelle Gray and will now swear		
18				18	in the witness.		
19				19	- - -		
20				20	... BROOKE T. MOSSMAN, M.S., Ph.D.,		
21				21	having been first duly sworn, was		
22				22	examined and testified as follows:		
23				23	- - -		
24				24	THE VIDEOGRAPHER: Please		

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Page 14	Page 16
<p>1 proceed.</p> <p>2 - - -</p> <p>3 EXAMINATION</p> <p>4 - - -</p> <p>5 BY MR. SMITH:</p> <p>6 Q. Good morning.</p> <p>7 A. Good morning.</p> <p>8 Q. How are you, Dr. Mossman?</p> <p>9 A. Fine, thank you.</p> <p>10 Q. We spoke on the phone on the</p> <p>11 Brower case; is that correct?</p> <p>12 A. We did.</p> <p>13 Q. And I have some questions</p> <p>14 for you here today. First thing is, I</p> <p>15 want to just attach, for reference, is</p> <p>16 the notice of your deposition, I'm going</p> <p>17 to attach as Exhibit 1.</p> <p>18 Have you -- have you seen</p> <p>19 this notice of deposition?</p> <p>20 A. I haven't.</p> <p>21 Q. All right.</p> <p>22 (Document marked for</p> <p>23 identification as Exhibit</p> <p>24 Mossman-1.)</p>	<p>1 to attach that as Exhibit 2.</p> <p>2 (Document marked for</p> <p>3 identification as Exhibit</p> <p>4 Mossman-2.)</p> <p>5 BY MR. SMITH:</p> <p>6 Q. I also was provided some</p> <p>7 supplemental -- I saw the materials that</p> <p>8 you considered that were attached to your</p> <p>9 report. And I was also provided</p> <p>10 supplemental materials considered. Are</p> <p>11 these additional materials that you</p> <p>12 considered in this case, besides the ones</p> <p>13 that are included in your report?</p> <p>14 A. Yes.</p> <p>15 MR. SMITH: I'll attach that</p> <p>16 as Exhibit 3.</p> <p>17 (Document marked for</p> <p>18 identification as Exhibit</p> <p>19 Mossman-3.)</p> <p>20 BY MR. SMITH:</p> <p>21 Q. And we'll go over your</p> <p>22 report in more detail in a little bit.</p> <p>23 Please state your name and</p> <p>24 occupation.</p>
Page 15	Page 17
<p>1 BY MR. SMITH:</p> <p>2 Q. Okay. All right. And</p> <p>3 pursuant to your notice of your</p> <p>4 deposition, your counsel provided some</p> <p>5 invoices. Did you provide those to your</p> <p>6 counsel for your time?</p> <p>7 A. My -- my assistant did.</p> <p>8 Yes.</p> <p>9 Q. And I have one bill that</p> <p>10 totals \$16,548. I have another bill that</p> <p>11 totals \$30,626. And then I have a third</p> <p>12 bill which totals \$27,151 -- wait --</p> <p>13 yeah, \$151.41.</p> <p>14 Is that -- or do these three</p> <p>15 bills constitute all of the time that you</p> <p>16 have billed in this case?</p> <p>17 A. It may not have accounted</p> <p>18 for my time in the last week or two. I'm</p> <p>19 not sure when these were sent out.</p> <p>20 Q. Absent your time in the past</p> <p>21 couple of weeks, would this cover the</p> <p>22 bills that you have billed in this case?</p> <p>23 A. I believe so, yes.</p> <p>24 MR. SMITH: Okay. I'm going</p>	<p>1 A. Brooke Taylor Mossman. I'm</p> <p>2 a university distinguished professor in</p> <p>3 the department of pathology.</p> <p>4 Q. Are you retired?</p> <p>5 A. Semi-retired, yes.</p> <p>6 Q. What does that mean?</p> <p>7 A. What it means is that I have</p> <p>8 an office at the university. I have some</p> <p>9 responsibilities through my office at the</p> <p>10 university, but am not being paid</p> <p>11 formally by the university anymore.</p> <p>12 Q. And your professional title</p> <p>13 is that of an experimental pathologist,</p> <p>14 correct?</p> <p>15 A. My professional title is a</p> <p>16 professor of pathology and laboratory</p> <p>17 medicine.</p> <p>18 Q. You were trained in lung</p> <p>19 pathology and disease associated with</p> <p>20 asbestos exposure; is that correct?</p> <p>21 A. That's correct.</p> <p>22 Q. And you do not have any</p> <p>23 prior training in ovarian cancer; is that</p> <p>24 correct?</p>

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<p style="text-align: right;">Page 18</p> <p>1 MR. FROST: Objection to 2 form. 3 THE WITNESS: Yeah. I 4 actually got a master's degree in 5 the department of obstetrics and 6 gynecology looking at cervical 7 cancer. 8 BY MR. SMITH: 9 Q. I'm talking about ovarian 10 cancer, ma'am. 11 A. I have not been trained in 12 ovarian cancer formally. 13 Q. You're not a medical doctor? 14 A. That's correct. 15 Q. And you also understand that 16 the issues involved in this case are not 17 that of cervical cancer but of ovarian 18 cancer? Do you understand that? 19 A. Yes, I do. 20 Q. You are not a diagnostic 21 pathologist, correct? 22 A. Correct. 23 Q. You're not an 24 epidemiologist, correct?</p>	<p style="text-align: right;">Page 20</p> <p>1 reproductive tract? 2 A. Yes, I've had formal courses 3 in my training on that. 4 Q. What formal courses of 5 training have you had on the female 6 reproductive tract? 7 A. I had a master's in 8 obstetrics and gynecology. And I had a 9 course -- actually it was an eight-credit 10 course which is a requirement for not 11 only the master's, but also medical 12 students who I took the course with. And 13 this covered anatomy of the entire body. 14 Q. So you had an eight-hour 15 course on human female anatomy? 16 A. No. An eight-hour course on 17 anatomy of every organ, of which female 18 anatomy was included. 19 MR. FROST: I object 20 belatedly to the form of that 21 question. 22 BY MR. SMITH: 23 Q. You are not a mineralogist; 24 is that correct?</p>
<p style="text-align: right;">Page 19</p> <p>1 A. No. But I am aware of the 2 epidemiological research which bolsters 3 my opinion in this case. 4 Q. Ma'am, are you an 5 epidemiologist? 6 A. I am not. 7 Q. You're not a gynecologist? 8 A. Correct. 9 Q. And you're not an 10 oncologist; is that correct? 11 A. Correct. 12 Q. You're not a gynecological 13 oncologist; is that correct? 14 A. That's correct. 15 Q. And you're not an expert in 16 anatomy and physiology; is that correct? 17 MR. FROST: Objection to 18 form. 19 THE WITNESS: Yeah, I have 20 been trained formally in medical 21 anatomy of the lung, yes. 22 BY MR. SMITH: 23 Q. How about of the rest of the 24 human body, such as the female</p>	<p style="text-align: right;">Page 21</p> <p>1 A. That's correct. 2 Q. You are not a geologist; is 3 that correct? 4 A. That's correct. 5 Q. You are not a materials 6 analyst; is that correct? 7 A. That's correct. 8 Q. Analyzing whether a sample 9 of material is talc, asbestos, or talc 10 with asbestos, you leave to the 11 mineralogists; is that correct? 12 A. That's correct. 13 Q. Same for determining if a 14 mineral is asbestos or asbestiform, you 15 would leave that to a mineralogist; is 16 that correct? 17 A. I would. 18 Q. You're not an expert in 19 determining the flexibility or rigidity 20 of asbestos or cleavage fragments; is 21 that correct? 22 A. That's correct. I don't 23 measure that. 24 Q. With regard to the</p>

6 (Pages 18 to 21)

Brooke T. Mossman, M.S., Ph.D.

<p style="text-align: right;">Page 22</p> <p>1 crystallinity of asbestos, cleavage 2 fragments, or talc, you are not an expert 3 in that area either, correct? 4 A. Correct. 5 Q. Same for surface properties. 6 You are not an expert in surface 7 properties of asbestos, cleavage 8 fragments, or talc; is that correct? 9 MR. FROST: Objection to 10 form. 11 THE WITNESS: I have 12 measured surface properties and 13 surface charge of materials in the 14 past. 15 BY MR. SMITH: 16 Q. Would you consider yourself 17 an expert in this area? 18 A. I think you have to clarify 19 what an expert in surface chemistry would 20 be. 21 Q. What would you define an 22 expert in surface chemistry to be? 23 A. I would describe that as 24 someone who has focused on an aspect of</p>	<p style="text-align: right;">Page 24</p> <p>1 BY MR. SMITH: 2 Q. Well, did you tell truthful 3 testimony in the Leavitt case in trial 4 and did you tell truthful testimony in 5 the Brower deposition? 6 A. Absolutely. 7 Q. Okay. So I can rely on that 8 testimony as being truthful, correct? 9 A. Yes. 10 Q. Okay. Thank you. 11 All right. If you'll look 12 at Page 83. 13 MR. FROST: You said 14 February 21? 15 MR. SMITH: Yep. 16 BY MR. SMITH: 17 Q. If you'll go to Line 8 and 18 it says, "Question: And similarly 19 surface properties of a particle, you 20 leave that to mineralogists as well, and 21 that's not an area within your expertise, 22 correct?" 23 And your answer was, "Again, 24 I should emphasize that one of the things</p>
<p style="text-align: right;">Page 23</p> <p>1 surface chemistry that's important. In 2 our case, we measured zeta potential or 3 surface charge of materials. 4 Q. Do you believe that your 5 work has -- that you are an expert in 6 this area because of your work in this 7 area? 8 A. I believe I'm an expert in 9 determining the surface charge of 10 materials that I have experimented with. 11 Q. Okay. Let's go to your 12 Leavitt deposition -- trial testimony, if 13 you wouldn't mind. It's on Page 83. And 14 it should be of the February session, 15 February 21st session. 16 Let me ask you this. Can I 17 rely on your prior trial testimony in the 18 Leavitt case and your prior deposition 19 testimony in the Brower case? 20 MR. FROST: Objection to 21 form. 22 THE WITNESS: Yeah, I'm not 23 sure what you mean, sir, in terms 24 of rely upon.</p>	<p style="text-align: right;">Page 25</p> <p>1 that we've done is looked at things such 2 as iron using this EDAX technique." 3 E-D-A-X. "So in that case, we have 4 looked at surface iron." 5 And question again: "Okay. 6 But other than looking at iron on the 7 surface of a particle, and we'll get into 8 that later, you determining surface 9 properties of a particular property of a 10 particular particle is not a matter 11 within your expertise, correct? 12 "I don't do that, yes, 13 that's correct." 14 Is that the correct answer? 15 MR. FROST: Objection to 16 form. 17 THE WITNESS: Yeah, surface 18 properties and surface charge are 19 two different things. Surface 20 charge being a subset of surface 21 properties. 22 So as I emphasize, I have 23 measured the surface charge of 24 materials, including talc, and</p>



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<p style="text-align: right;">Page 26</p> <p>1 that has been published.</p> <p>2 BY MR. SMITH:</p> <p>3 Q. Can I rely on your testimony</p> <p>4 that I just read in Leavitt as accurate</p> <p>5 and truthful?</p> <p>6 MR. FROST: Objection to</p> <p>7 form.</p> <p>8 THE WITNESS: In terms of</p> <p>9 iron, yes.</p> <p>10 BY MR. SMITH:</p> <p>11 Q. Thank you.</p> <p>12 Have you ever diagnosed or</p> <p>13 treated a person with mesothelioma?</p> <p>14 A. I have not.</p> <p>15 Q. Have you ever diagnosed or</p> <p>16 treated a person with ovarian cancer?</p> <p>17 A. I have not.</p> <p>18 Q. Have you ever been called</p> <p>19 upon to determine what caused a person's</p> <p>20 mesothelioma?</p> <p>21 A. You'll have to be a little</p> <p>22 more explicit. What do you mean by</p> <p>23 called upon?</p> <p>24 Q. Can you go to your Leavitt</p>	<p style="text-align: right;">Page 28</p> <p>1 Is that true?</p> <p>2 A. Yes.</p> <p>3 Q. And next question: "You've</p> <p>4 never been involved in the care and</p> <p>5 treatment of a person with mesothelioma,</p> <p>6 correct?"</p> <p>7 "I have not treated them,</p> <p>8 that's correct. I have been</p> <p>9 involved in studying drugs that</p> <p>10 help them though."</p> <p>11 Is that correct?</p> <p>12 A. That's correct.</p> <p>13 Q. Would the same be for a</p> <p>14 person that's been diagnosed with ovarian</p> <p>15 cancer, have you ever diagnosed or</p> <p>16 treated a person with ovarian cancer?</p> <p>17 A. I have not.</p> <p>18 Q. And you have not diagnosed a</p> <p>19 person with mesothelioma, correct?</p> <p>20 MR. FROST: Objection, asked</p> <p>21 and answered.</p> <p>22 THE WITNESS: Yeah.</p> <p>23 BY MR. SMITH:</p> <p>24 Q. And you have never diagnosed</p>
<p style="text-align: right;">Page 27</p> <p>1 testimony Page 78.</p> <p>2 A. Mm-hmm.</p> <p>3 Q. It says, "Question: You</p> <p>4 have never diagnosed mesothelioma in a</p> <p>5 human being?</p> <p>6 "That's correct."</p> <p>7 Is that true?</p> <p>8 MR. FROST: I'm sorry,</p> <p>9 what -- where are you?</p> <p>10 THE WITNESS: Yeah, I'm --</p> <p>11 BY MR. SMITH:</p> <p>12 Q. Page -- I'm sorry, Page 78,</p> <p>13 Line 11 through 13.</p> <p>14 MR. FROST: Okay.</p> <p>15 THE WITNESS: Okay.</p> <p>16 BY MR. SMITH:</p> <p>17 Q. "Question: And you've never</p> <p>18 been diagnosed" -- "you've never" --</p> <p>19 excuse me.</p> <p>20 "Question: And you have</p> <p>21 never diagnosed mesothelioma in any human</p> <p>22 being, correct?"</p> <p>23 Your answer was, "That's</p> <p>24 correct."</p>	<p style="text-align: right;">Page 29</p> <p>1 a person with ovarian cancer, correct?</p> <p>2 MR. FROST: Same objection.</p> <p>3 THE WITNESS: That's</p> <p>4 correct.</p> <p>5 BY MR. SMITH:</p> <p>6 Q. And the levels of exposure</p> <p>7 of each type of asbestos in terms of</p> <p>8 human risk are outside of your area of</p> <p>9 expertise; is that correct?</p> <p>10 MR. FROST: Objection to</p> <p>11 form.</p> <p>12 THE WITNESS: Yeah. You're</p> <p>13 going to have to be a little -- a</p> <p>14 little more specific on that. I</p> <p>15 don't --</p> <p>16 BY MR. SMITH:</p> <p>17 Q. Okay. Let's go to Leavitt</p> <p>18 testimony Page 92.</p> <p>19 All right. Starting on</p> <p>20 page -- excuse me, Page 92, Line 10.</p> <p>21 "Question: As then you can</p> <p>22 see on the next page and a half, the</p> <p>23 lawyer asked you about each type of</p> <p>24 asbestos, crocidolite, amosite,</p>

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<p>1 tremolite, actinolite, anthophyllite, 2 chrysotile. Did you see that?" 3 And your answer was, "I do." 4 "Question: And each time 5 you said that that was outside of your 6 area of expertise? 7 "Answer: Yes, the levels of 8 exposure of these in terms of human risk 9 are outside of my area of expertise." 10 Is that truthful testimony 11 and can I rely on that today? 12 MR. FROST: Objection to 13 form. 14 THE WITNESS: Yeah. That's 15 truthful, my statement is 16 truthful. 17 BY MR. SMITH: 18 Q. Thank you. 19 Is it important to 20 understand cancer development? 21 MR. FROST: Objection to 22 form. 23 MR. SMITH: What's the 24 matter with the form of the</p>	<p>1 A. I'm getting there. 2 Q. And if you'll focus in on 3 Line 14. 4 "Question: Is it important 5 to understand cancer development in your 6 opinion? 7 "Answer: Yes." 8 Can I rely on that testimony 9 as truthful? 10 MR. FROST: Objection to 11 form. 12 THE WITNESS: Yes, it was a 13 very broad question, but in 14 general, yes, the answer's 15 correct. 16 BY MR. SMITH: 17 Q. Cell cultures or in vitro 18 studies are valuable in determining 19 mechanisms on cancer causation, correct? 20 A. Yes. They're part of the 21 hierarchy of studying different elements 22 of or models of cancer development. 23 Q. One way to determine if 24 biological mechanisms or pathways are</p>
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<p>1 question? 2 MR. FROST: I don't 3 understand what you mean by 4 "important to understand cancer 5 development." 6 BY MR. SMITH: 7 Q. Do you understand what I 8 mean by "it's important to understand 9 cancer development," Doctor? 10 A. It -- it's very broad. 11 It's -- it's important for what? 12 Q. Let's go to your deposition 13 testimony in Brower. 14 A. Okay. 15 Q. You got that in front of 16 you, Doctor? 17 A. I -- I think that's Leavitt. 18 MR. FROST: I believe this 19 is it. October 26th. 20 It fell apart. 21 BY MR. SMITH: 22 Q. Page 49, Doctor. You there? 23 A. I am not yet, sorry. 24 Q. That's okay.</p>	<p>1 triggered is to conduct in vitro studies 2 of relevant cells of disease and exposure 3 to the questioned substance; is that 4 correct? 5 A. Yes. 6 Q. You would agree with me that 7 it is important to identify and, if 8 possible, eliminate substances that 9 increase human risk of contracting 10 cancer? 11 MR. FROST: Objection to 12 form. 13 MR. SMITH: What's the 14 matter with the form? 15 MR. FROST: Again, I think 16 it's very vague to identify 17 impossible -- or important to 18 identify impossible to eliminate 19 substances. Compound question. 20 It's also vague as to what you 21 mean by important. 22 BY MR. SMITH: 23 Q. Do you understand the 24 question, Doctor?</p>

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<p>1 A. I don't.</p> <p>2 Q. Why don't we go to your</p> <p>3 deposition testimony in Brower. Page 49.</p> <p>4 Question, Line 6: "I'm asking in</p> <p>5 general, is it important as a scientist</p> <p>6 to identify and, if possible, eliminate</p> <p>7 any substances, if possible, that</p> <p>8 increase the risk of ovarian -- excuse</p> <p>9 me -- of contracting cancer?"</p> <p>10 And your answer was, "Yes,</p> <p>11 in principle."</p> <p>12 Can I rely on that as</p> <p>13 truthful?</p> <p>14 A. Yes.</p> <p>15 MR. FROST: I'll also lodge</p> <p>16 the same question that Mr. Bishop</p> <p>17 lodged to that question in that</p> <p>18 deposition.</p> <p>19 BY MR. SMITH:</p> <p>20 Q. Chronic inflammation and</p> <p>21 oxidative stress are two mechanisms that</p> <p>22 promote tumor and cancer development in</p> <p>23 known carcinogens; is that correct?</p> <p>24 A. That is true with regard to</p>	<p>1 BY MR. SMITH:</p> <p>2 Q. I understand potency. And</p> <p>3 we talked about potency and how</p> <p>4 crocidolite is more potent than, say,</p> <p>5 chrysotile. And that's not what I'm</p> <p>6 talking about, Doctor.</p> <p>7 You would agree with me that</p> <p>8 all types of asbestos are carcinogenic to</p> <p>9 human beings, correct?</p> <p>10 MR. FROST: Objection to</p> <p>11 form.</p> <p>12 THE WITNESS: Not really. I</p> <p>13 wouldn't agree with you without</p> <p>14 qualifying that statement with</p> <p>15 regard to consideration -- for</p> <p>16 example, IARC does consider all</p> <p>17 types of asbestos as carcinogenic.</p> <p>18 But as a scientist, it</p> <p>19 depends upon the type of asbestos</p> <p>20 and the dose that determines</p> <p>21 whether or not it's a carcinogen.</p> <p>22 BY MR. SMITH:</p> <p>23 Q. So you're saying that not</p> <p>24 all types of asbestos are carcinogenic to</p>
Page 35	Page 37
<p>1 certain types of asbestos, correct.</p> <p>2 Q. And other known carcinogens,</p> <p>3 correct?</p> <p>4 A. The only carcinogen in terms</p> <p>5 of chronic inflammation that I'm aware of</p> <p>6 has been cigarette smoke.</p> <p>7 Q. And we'll talk about chronic</p> <p>8 inflammation and oxidative stress later.</p> <p>9 But asbestos is a known carcinogen,</p> <p>10 correct?</p> <p>11 A. That, again, is a very broad</p> <p>12 statement. Asbestos types vary in their</p> <p>13 potency for cancer.</p> <p>14 Q. All types of asbestos,</p> <p>15 regardless of type, are human</p> <p>16 carcinogens, correct?</p> <p>17 MR. FROST: Objection to</p> <p>18 form.</p> <p>19 THE WITNESS: Again, I want</p> <p>20 to emphasize that it's a hierarchy</p> <p>21 of effects, and it depends upon</p> <p>22 the tumors that you're talking</p> <p>23 about.</p> <p>24</p>	<p>1 human beings?</p> <p>2 MR. FROST: Objection to</p> <p>3 form.</p> <p>4 THE WITNESS: I'm saying</p> <p>5 that there are many types of</p> <p>6 tumors in humans, that with regard</p> <p>7 to asbestos there are certain</p> <p>8 types that are associated with</p> <p>9 asbestos exposures at high</p> <p>10 concentrations.</p> <p>11 BY MR. SMITH:</p> <p>12 Q. My question is just really</p> <p>13 more simple. I understand that you can</p> <p>14 have levels of exposure and potency of</p> <p>15 different types of asbestos. But do you</p> <p>16 consider crocidolite a human carcinogen?</p> <p>17 A. I do.</p> <p>18 Q. Do you consider chrysotile a</p> <p>19 human carcinogen?</p> <p>20 A. I do with regard to lung</p> <p>21 cancer. I think it's very questionable</p> <p>22 with regards to mesothelioma.</p> <p>23 Q. What about actinolite? Do</p> <p>24 you consider that a human carcinogen?</p>

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<p>1 MR. FROST: Object to form.</p> <p>2 THE WITNESS: Yeah. I don't</p> <p>3 think that there is any human data</p> <p>4 available to classify actinolite</p> <p>5 as a human carcinogen.</p> <p>6 BY MR. SMITH:</p> <p>7 Q. And IARC and NTP disagree</p> <p>8 with your assessment on that, don't they?</p> <p>9 MR. FROST: Objection to</p> <p>10 form. Misstates document.</p> <p>11 THE WITNESS: Yeah. Let me</p> <p>12 just state that I think both</p> <p>13 agencies would consider that there</p> <p>14 are no data in humans on</p> <p>15 actinolite to prove its</p> <p>16 carcinogenicity.</p> <p>17 BY MR. SMITH:</p> <p>18 Q. There have been formal</p> <p>19 statements by the national toxicology</p> <p>20 program of the United States, and in a</p> <p>21 monograph by IARC that say that all types</p> <p>22 of asbestos are human carcinogens. You</p> <p>23 know that, Doctor, correct?</p> <p>24 A. I do.</p>	<p>1 disagree with NTP and IARC if they</p> <p>2 classify all types of asbestos, every</p> <p>3 single one of them, as a human</p> <p>4 carcinogen, and you're telling me</p> <p>5 actinolite, there's not data to support</p> <p>6 it's a carcinogen? How are you not</p> <p>7 disagreeing with the NTP and IARC on that</p> <p>8 matter then?</p> <p>9 MR. FROST: Objection to</p> <p>10 form.</p> <p>11 THE WITNESS: I don't</p> <p>12 believe they have statements on</p> <p>13 different types of asbestos such</p> <p>14 as actinolite.</p> <p>15 BY MR. SMITH:</p> <p>16 Q. Okay. We'll go get to that</p> <p>17 in a minute. Does -- do you consider</p> <p>18 tremolite a human carcinogen?</p> <p>19 MR. FROST: Objection to</p> <p>20 form.</p> <p>21 THE WITNESS: Again, it</p> <p>22 depends on the type of tumor you</p> <p>23 are talking about and the dose of</p> <p>24 the material and the form.</p>
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<p>1 MR. FROST: Objection to</p> <p>2 form.</p> <p>3 BY MR. SMITH:</p> <p>4 Q. So --</p> <p>5 A. But that -- but let me just</p> <p>6 emphasize here that lumping asbestos into</p> <p>7 one category has been necessary in terms</p> <p>8 of risk assessment, but in terms of</p> <p>9 biological effects, that statement may</p> <p>10 not be true, especially in humans.</p> <p>11 Q. So you disagree with the</p> <p>12 assessment of the national toxicology</p> <p>13 program for the United States government</p> <p>14 and IARC on this matter?</p> <p>15 MR. FROST: Objection to</p> <p>16 form. Misstates the document.</p> <p>17 THE WITNESS: I don't</p> <p>18 disagree. I'm just saying that</p> <p>19 there are no data scientifically</p> <p>20 to support the premise that</p> <p>21 something like actinolite asbestos</p> <p>22 is a human carcinogen.</p> <p>23 BY MR. SMITH:</p> <p>24 Q. Well, how do you not</p>	<p>1 BY MR. SMITH:</p> <p>2 Q. Can it cause cancer in human</p> <p>3 beings?</p> <p>4 MR. FROST: Objection to</p> <p>5 form.</p> <p>6 THE WITNESS: If you're</p> <p>7 talking about tremolite asbestos,</p> <p>8 there is some data suggesting,</p> <p>9 yes, that it can cause</p> <p>10 mesothelioma.</p> <p>11 BY MR. SMITH:</p> <p>12 Q. What about anthophyllite?</p> <p>13 MR. FROST: Same objection.</p> <p>14 THE WITNESS: Yeah. A very</p> <p>15 weak carcinogen compared to</p> <p>16 crocidolite or amosite, certainly</p> <p>17 in mesothelioma.</p> <p>18 BY MR. SMITH:</p> <p>19 Q. So you believe that all</p> <p>20 types of asbestos are human carcinogens</p> <p>21 except actinolite?</p> <p>22 MR. FROST: Objection to</p> <p>23 form. Misstates testimony.</p> <p>24 THE WITNESS: No, that's not</p>

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<p>1 what I'm saying. I'm saying that</p> <p>2 if one looks at the scientific</p> <p>3 data on human population, there's</p> <p>4 not clear-cut information on the</p> <p>5 doses of certain materials such as</p> <p>6 tremolite, such as actinolite, in</p> <p>7 terms of carcinogenic effects.</p> <p>8 BY MR. SMITH:</p> <p>9 Q. Again, back to my question.</p> <p>10 Chronic inflammation and oxidative stress</p> <p>11 are two mechanisms that promote tumor and</p> <p>12 cancer development in known carcinogens;</p> <p>13 is that correct?</p> <p>14 MR. FROST: Objection to</p> <p>15 form. Asked and answered.</p> <p>16 THE WITNESS: Yeah. I</p> <p>17 emphasize that that's known or</p> <p>18 certainly accepted for things such</p> <p>19 as asbestos, amphibole types of</p> <p>20 asbestos, as well as cigarette</p> <p>21 smoke.</p> <p>22 BY MR. SMITH:</p> <p>23 Q. Oxidants stimulate protein</p> <p>24 pathways that then cause the cell to</p>	<p>1 A. Those are pathways that</p> <p>2 we've studied, yes.</p> <p>3 Q. And you stated you do not</p> <p>4 need all of these factors to cause</p> <p>5 cancer; is that right?</p> <p>6 A. I think you need to be a</p> <p>7 little more explicit.</p> <p>8 Q. Well, let's look at your</p> <p>9 Leavitt testimony Page 133.</p> <p>10 A. Okay.</p> <p>11 Q. Let's see. Question on</p> <p>12 Line 8. "Now, you mention there were</p> <p>13 four different kinds, four different</p> <p>14 markers of asbestos, I mean of cancer.</p> <p>15 And asbestos causes all four of these</p> <p>16 markers to current cells?</p> <p>17 "Answer: Yes. And this</p> <p>18 gives you an idea of the different types</p> <p>19 of things we've studied. It's like the</p> <p>20 lock, and once that is unlocked, you get</p> <p>21 the development of cancer. And here we</p> <p>22 see where healthy cells become cancer</p> <p>23 cell and then that the cancer cell</p> <p>24 divides to become a malignant tumor.</p>
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<p>1 transform and become a tumor, correct?</p> <p>2 MR. FROST: Objection to</p> <p>3 form.</p> <p>4 THE WITNESS: That's some of</p> <p>5 the work that we've done, yes.</p> <p>6 BY MR. SMITH:</p> <p>7 Q. And antioxidant --</p> <p>8 antioxidants are kicked in by a cell</p> <p>9 after exposure to low doses of an</p> <p>10 environmental agent as the doses become</p> <p>11 chronic or at higher concentration, the</p> <p>12 cells become overwhelmed and not able to</p> <p>13 correct the imbalance and then protein</p> <p>14 receptors on the cell are affected and</p> <p>15 cause the cell to transform; is that</p> <p>16 correct?</p> <p>17 A. That's true in some cases,</p> <p>18 yes.</p> <p>19 Q. And you talked about a</p> <p>20 four-step process to mesothelioma before,</p> <p>21 Doctor; is that correct, oxidant release,</p> <p>22 protein receptor changes, genome-wide</p> <p>23 expression changes and cell -- cell</p> <p>24 proliferation, correct?</p>	<p>1 "Let me ask you. If you</p> <p>2 only have three of the four markers, will</p> <p>3 you still have a mutation of that cell</p> <p>4 that causes cancer?</p> <p>5 "You may, but you won't have</p> <p>6 the entire process mimicked. So you need</p> <p>7 all four of these features of asbestos</p> <p>8 fibers to induce a cell, a healthy cell</p> <p>9 to become a malignant cell."</p> <p>10 Is that truthful testimony</p> <p>11 and can I rely on that?</p> <p>12 A. Yes, that's true.</p> <p>13 Q. Do you know which of these</p> <p>14 steps is necessary to cause ovarian</p> <p>15 cancer?</p> <p>16 A. No, I don't.</p> <p>17 Q. Of the four-step process you</p> <p>18 said to mesothelioma, and I'm going to</p> <p>19 refer to it like we did in Brower. Is it</p> <p>20 okay if I refer to the Shukla study by</p> <p>21 the first author Shukla, and then</p> <p>22 Hillegass by Hillegass? Is that fair?</p> <p>23 A. Yes.</p> <p>24 Q. Okay. In the Shukla study</p>

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<p>1 you saw gene expression changes with talc 2 compared to neo mesothelial cells, 3 correct? 4 A. Could you repeat that again? 5 Q. Sure. In Shukla you saw 30 6 gene expression changes to talc compared 7 to neo mesothelial cells at the 8 75 micrometers per centimeter squared 9 concentration for eight hours, correct? 10 A. Yes. 11 Q. And -- but you never tested 12 talc in that study or in the Hillegass 13 study that came after it for oxidant 14 release, correct? 15 A. Could you repeat that again? 16 We've never tested cells for oxidant 17 release? 18 Q. In Hillegass, you did a 19 bunch of further studies on crocidolite 20 asbestos that you did not do on talc, 21 correct? 22 A. We only did additional 23 studies where we focused on the proteins 24 that were increased by asbestos. Many of</p>	<p>1 it was a transient change of gene 2 expression changes or not, fair? 3 MR. FROST: Objection to 4 form. 5 THE WITNESS: Yeah, we -- we 6 did not test asbestos or talc at 7 the highest concentration because 8 of cell death in the asbestos 9 exposed cultures. That's correct. 10 BY MR. SMITH: 11 Q. So you cannot tell me what 12 genes were altered or if they were more 13 altered at the higher concentration at 14 24 hours for talc that you saw at the 15 higher concentration at eight hours, 16 correct? 17 MR. FROST: Objection to 18 form. 19 THE WITNESS: We did not, 20 because they were -- I cannot tell 21 you that, because we didn't look 22 at talc for the reasons that I 23 just stated. 24 BY MR. SMITH:</p>
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<p>1 these were not increased by talc. 2 Q. Ma'am, that's not my 3 question. 4 A. Okay. 5 Q. My question was, you did not 6 do all of the studies, all of those 7 assays and all of the protein 8 determination and all of that in 9 Hillegass. You did that for crocidolite 10 asbestos. You did not do talc in that 11 study? 12 MR. FROST: Objection to 13 form. 14 THE WITNESS: Yeah, and I 15 emphasize we didn't do talc, 16 because we didn't see that these 17 changes were protracted. 18 BY MR. SMITH: 19 Q. Well, ma'am, you did not 20 test talc at 24 hours at the higher 21 concentration -- 22 MR. FROST: Objection. 23 BY MR. SMITH: 24 Q. -- so you don't know whether</p>	<p>1 Q. And we'll talk more about 2 the studies in more detail in a minute. 3 In the Shukla study, you saw 4 the gene expression changes at eight 5 hours at the higher concentration 6 compared to -- compared to neo 7 mesothelial cells, correct? 8 MR. FROST: Objection to 9 form. 10 THE WITNESS: We saw 30 11 genes that were increased by 12 highest concentrations of talc. 13 BY MR. SMITH: 14 Q. But you never tested talc in 15 oxidant release of peritoneal mesothelial 16 cells in that study -- either one of 17 those studies, correct? 18 A. That's correct. 19 Q. And you did not test talc 20 for protein receptor changes in any of 21 those cells in either one of those 22 studies, correct? 23 A. We did -- 24 MR. FROST: Objection to</p>



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<p>1 form.</p> <p>2 THE WITNESS: Yeah, we</p> <p>3 didn't test talc because it didn't</p> <p>4 indicate genes that were increased</p> <p>5 that were related to oxidative</p> <p>6 stress, or the proteins that we</p> <p>7 were interested in that were</p> <p>8 increased by asbestos.</p> <p>9 BY MR. SMITH:</p> <p>10 Q. You're telling me ATF3 and</p> <p>11 IL-8 are not associated of mediating</p> <p>12 inflammatory or oxidative processes in</p> <p>13 the cell?</p> <p>14 MR. FROST: Objection to</p> <p>15 form.</p> <p>16 THE WITNESS: ATF3 as we</p> <p>17 showed in the -- in the Shukla</p> <p>18 study is a gene that repairs cells</p> <p>19 from cytokine production.</p> <p>20 BY MR. SMITH:</p> <p>21 Q. Again, you did not test talc</p> <p>22 for protein receptor changes when applied</p> <p>23 to peritoneal mesothelial cells in either</p> <p>24 one of the two studies, correct?</p>	<p>1 you read that again?</p> <p>2 MR. FROST: Yeah, I was</p> <p>3 going to say, do you mind</p> <p>4 repeating that one?</p> <p>5 BY MR. SMITH:</p> <p>6 Q. Sure.</p> <p>7 Protein receptors have</p> <p>8 chains that bind to cellular DNA, causing</p> <p>9 changes to genes in the DNA to create an</p> <p>10 abnormal cell which can lead to cancer,</p> <p>11 correct?</p> <p>12 A. That can be one endpoint of</p> <p>13 a protein receptor.</p> <p>14 Q. And there's a test for that,</p> <p>15 correct, a test to see which genes are</p> <p>16 upregulated or downregulated, correct?</p> <p>17 A. Genes but not proteins.</p> <p>18 Q. Correct. Cell proliferation</p> <p>19 is a hallmark of cancer causing</p> <p>20 substances and there are tools to look at</p> <p>21 cell division and assays to look at</p> <p>22 clumps of cells to see if they survive</p> <p>23 and become uncontrolled and lead to</p> <p>24 cancer; is that correct?</p>
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<p>1 A. We didn't test anything for</p> <p>2 protein receptor changes in either of</p> <p>3 those studies. We were interested in</p> <p>4 gene expression.</p> <p>5 Q. And for talc in either one</p> <p>6 of those studies regarding peritoneal</p> <p>7 mesothelial cells, you did not check for</p> <p>8 cell proliferation, correct?</p> <p>9 A. Yes, we did not see genes</p> <p>10 that were indicative of cell</p> <p>11 proliferation by talc -- and we didn't</p> <p>12 test --</p> <p>13 Q. Did you test for gene -- did</p> <p>14 you test?</p> <p>15 A. No, we didn't see changes</p> <p>16 that were indicated at the gene level.</p> <p>17 Q. Protein receptors that have</p> <p>18 chains that bind to cellular DNA causing</p> <p>19 changes to genes in the DNA to create</p> <p>20 abnormal cell -- cells which can lead to</p> <p>21 cancer; is that correct?</p> <p>22 MR. FROST: Objection to</p> <p>23 form.</p> <p>24 THE WITNESS: Yeah, could</p>	<p>1 MR. FROST: Objection to</p> <p>2 form.</p> <p>3 THE WITNESS: Yeah, can we</p> <p>4 go through that piece by piece?</p> <p>5 BY MR. SMITH:</p> <p>6 Q. Sure. Is cell proliferation</p> <p>7 a hallmark of cancer-causing substances?</p> <p>8 MR. FROST: Objection to</p> <p>9 form.</p> <p>10 THE WITNESS: Not all of</p> <p>11 them. Some substances don't</p> <p>12 induce cell proliferation. They</p> <p>13 act with DNA directly.</p> <p>14 BY MR. SMITH:</p> <p>15 Q. You told me earlier there</p> <p>16 was a four-step process to mesothelioma,</p> <p>17 correct, and one of them was cell</p> <p>18 proliferation; is that right?</p> <p>19 A. These are changes that we</p> <p>20 have studied called epigenetic, meaning</p> <p>21 that they don't occur at the level of the</p> <p>22 DNA. And that's been the focus of our</p> <p>23 lab.</p> <p>24 I don't want to give you the</p>

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<p>1 impression that that's the only way that</p> <p>2 mesothelioma develops. That's what we</p> <p>3 focused on.</p> <p>4 Q. All right. Maybe a better</p> <p>5 term is cell proliferation is a</p> <p>6 characteristic of a cancer-causing</p> <p>7 substance. Would you agree with that?</p> <p>8 A. No, I wouldn't.</p> <p>9 As I mentioned, there are a</p> <p>10 lot of agents that don't induce cell</p> <p>11 proliferation that cause cancer.</p> <p>12 Q. Does -- does asbestos induce</p> <p>13 cell proliferation or cause it?</p> <p>14 A. It depends upon the type and</p> <p>15 the dose. Again, we've shown that for</p> <p>16 crocidolite and amosite asbestos in our</p> <p>17 models.</p> <p>18 Q. We don't know why some</p> <p>19 carcinogens are site-specific in the</p> <p>20 human body, correct?</p> <p>21 A. That's a broad statement.</p> <p>22 But yes, we know -- we don't know why</p> <p>23 some agents aren't site specific.</p> <p>24 Q. SNPs or single nucleotide</p>	<p>1 to be one mechanism, whereas some</p> <p>2 hereditary cancers or cancers due to</p> <p>3 agents that focus on the break of DNA</p> <p>4 exert their effects."</p> <p>5 Can I rely on that answer?</p> <p>6 A. Yes.</p> <p>7 MR. FROST: Objection to</p> <p>8 form.</p> <p>9 BY MR. SMITH:</p> <p>10 Q. Thank you. You talked about</p> <p>11 ATF3 a minute ago. But ATF3 is a gene,</p> <p>12 and it's also a transcription factor,</p> <p>13 right?</p> <p>14 A. It's a gene, it's a protein,</p> <p>15 and it's a transcription factor.</p> <p>16 Q. And would you agree with me</p> <p>17 that ATF3 is a gene -- the ATF3 gene is</p> <p>18 important in combatting inflammation in</p> <p>19 cells?</p> <p>20 MR. FROST: Objection to</p> <p>21 form.</p> <p>22 THE WITNESS: It depends</p> <p>23 upon the cell and the other</p> <p>24 transcription factors. In our</p>
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<p>1 polymorphisms, are mechanisms where some</p> <p>2 cancers due to exposure to agents can</p> <p>3 cause DNA changes that could lead to</p> <p>4 cancer development, correct?</p> <p>5 MR. FROST: Objection to</p> <p>6 form.</p> <p>7 THE WITNESS: Yes, SNPs are</p> <p>8 generally something that occurs in</p> <p>9 a population of cells. It's very</p> <p>10 unusual. In fact, I've never seen</p> <p>11 an agent such as asbestos that</p> <p>12 induces an SNP.</p> <p>13 BY MR. SMITH:</p> <p>14 Q. Can you go to your Brower</p> <p>15 deposition, please, ma'am.</p> <p>16 Page 87. If you'll go down</p> <p>17 to Line 13.</p> <p>18 "Question: What are SNPs or</p> <p>19 SNiPs or single nucleotide polymorphisms?</p> <p>20 "Answer: Those are changes</p> <p>21 in DNA.</p> <p>22 "Question: And how do they</p> <p>23 influence the development of cancer?</p> <p>24 "Answer: They are thought</p>	<p>1 experiments, we showed that it</p> <p>2 combatted changes by asbestos;</p> <p>3 that is, it decreased cytokines</p> <p>4 that are associated with</p> <p>5 development of tumors or immune</p> <p>6 response.</p> <p>7 BY MR. SMITH:</p> <p>8 Q. I'm going to ask you, I'm</p> <p>9 going to read a sentence to you and ask</p> <p>10 if you agree with it. "Stress-inducible</p> <p>11 transcription factors play a pivotal role</p> <p>12 in cellular adaptation to environment, to</p> <p>13 maintain homeostasis, and integrity of</p> <p>14 the genome."</p> <p>15 Would you agree with that</p> <p>16 statement?</p> <p>17 MR. FROST: Object to form.</p> <p>18 And I also object to you reading</p> <p>19 her sentences from a document that</p> <p>20 you haven't given her.</p> <p>21 Thank you.</p> <p>22 MR. SMITH: Sure.</p> <p>23 THE WITNESS: Thank you.</p> <p>24</p>

15 (Pages 54 to 57)



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<p style="text-align: right;">Page 58</p> <p>1 BY MR. SMITH: 2 Q. This is attached as 3 Exhibit 4. 4 (Document marked for 5 identification as Exhibit 6 Mossman-4.) 7 BY MR. SMITH: 8 Q. "Systems analysis of ATF3 9 and stress response in cancer reveals 10 opposing effects on pro-apoptotic genes 11 in p53 pathway." 12 Do you have that in front of 13 you, Doctor? 14 A. I do. 15 Q. I've attached it as 16 Exhibit 4. The first sentence in the 17 blue box under abstract. It says, 18 "Stress-inducible transcription factors 19 play a pivotal role in cellular 20 adaptation to environment to maintain 21 homeostasis and integrity in the genome." 22 Would you agree with that? 23 A. Yes. 24 Q. "Activating transcription</p>	<p style="text-align: right;">Page 60</p> <p>1 emphasized previously, it would depend 2 upon the type of cell in terms of the 3 effects on that cell type. 4 Q. Would you agree that ATF3 is 5 activated in response to oxidative stress 6 in a cell? 7 A. I would have to review that 8 literature. I don't see that statement 9 here. 10 Q. I'm asking you just the 11 question. 12 A. ATF3 and oxidative stress, I 13 can't recall specific experiments or cell 14 types that oxidants have been added to, 15 such as hydrogen peroxide or those 16 typical to oxidative stress in studies. 17 Q. IL-8 is a cytokine produced 18 during inflammation by lymphocytes; is 19 that correct? 20 A. It's one of the effects. It 21 also can have opposite effects. 22 Q. You've done a study on EMPs 23 or elongated mineral particles; is that 24 correct?</p>
<p style="text-align: right;">Page 59</p> <p>1 factor 3, or ATF3, is induced by a 2 variety of stress and inflammatory 3 conditions and is overexposed in many 4 kind of cancer cells." 5 Would you agree with that? 6 MR. FROST: Objection to 7 form. It's overexpressed. 8 MR. SMITH: That's what I 9 said. 10 MR. FROST: You said 11 overexposed. 12 BY MR. SMITH: 13 Q. Okay. Excuse me. Let me 14 read it again. Second sentence. 15 "Activating transcription factor 3, ATF3, 16 is induced by a variety of stress and 17 inflammatory conditions and is 18 overexpressed in many kinds of cancer 19 cells." 20 Would you agree with that? 21 A. I would agree with the first 22 part of that statement. 23 I have not seen the data on 24 many kinds of cancer cells, and as I</p>	<p style="text-align: right;">Page 61</p> <p>1 A. A study? I have done many 2 studies on elongated mineral particles. 3 Q. I was thinking of your most 4 recent study. But you have done several 5 studies on EMPs, correct? 6 A. Elongated mineral particles 7 including asbestos are -- have been 8 subject of my research for over 40 years. 9 Q. And it can be of any type of 10 mineral with certain dimensions that are 11 fibrous in nature that, when in contact 12 with human cells, can cause adverse 13 changes including epigenetic changes that 14 are pathways that can potentially lead to 15 carcinogenesis; is that correct? 16 MR. FROST: Objection to 17 form. 18 THE WITNESS: Yeah, can we 19 pick that statement apart? 20 BY MR. SMITH: 21 Q. Sure. Let's go to the 22 Brower deposition, Page 85. 23 A. Okay. 24 Q. And I'm going to read over</p>

16 (Pages 58 to 61)

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<p style="text-align: right;">Page 62</p> <p>1 two pages, 85, 86 and 87.  2 "Question: What is an EMP?  3 "An EMP is a very broad term  4 for elongated mineral particles, and it  5 could be referring to anything --  6 regardless of whether anything of certain  7 dimensions that are fibrous in nature.  8 It is a term that has been used most  9 recently by some regulatory agencies, but  10 it is very broad in terms of an umbrella  11 of materials that fit into this category.  12 "Question: And I note in  13 your paper that it says EMPs, and you  14 talk about long EMPs greater than 5  15 micrometers in length; is that correct?  16 "That's a cutoff" --  17 answer, excuse me.  18 "That's a cutoff that's been  19 used in terms of fibers that are thought  20 to be important in regulation. It's a  21 term that is controversial to biologists  22 and chemists.  23 "Question: Is it true that  24 by cell's direct contact with EMP, it</p>	<p style="text-align: right;">Page 64</p> <p>1 do you focus on" -- well, I think we've  2 moved on from EMPs."  3 But can I rely on that  4 testimony regarding EMPs?  5 A. Yes.  6 MR. FROST: And I'm just  7 going to lodge the same objections  8 that were in the transcript.  9 BY MR. SMITH:  10 Q. And can EMPs -- can they  11 cause adverse changes, including  12 epigenetic changes that are pathways that  13 could potentially lead to carcinogenesis?  14 A. Can EMPs? Certain ones  15 certainly can.  16 Q. Different grades of talc and  17 asbestos are different and distinct in  18 shape, size, crystallinity and structure;  19 is that correct?  20 MR. FROST: Objection to  21 form. Vague.  22 BY MR. SMITH:  23 Q. Let's break it out.  24 Different grades of talc are</p>
<p style="text-align: right;">Page 63</p> <p>1 causes the cell to react in certain ways?  2 "Answer: Direct contact by  3 any material can cause certain changes in  4 cells, yes.  5 "Question: And cellular  6 reactions to EMP has occurred, would you  7 agree without the EMP binding to any  8 cellular receptors or penetrating the  9 cell itself, correct?  10 "Answer: Could you just  11 state that again? I'm sorry.  12 "Sure.  13 "I missed the first part."  14 Answer.  15 Question: Sure. The  16 cellular reactions that we just discussed  17 to EMPs, they can occur without the EMP  18 binding to any cellular receptors or  19 penetrating the cell?"  20 And your answer was -- and  21 my question was, "Correct?"  22 And the answer was, "Yes."  23 I said, "Question: Okay,  24 what is the function of proteins and why</p>	<p style="text-align: right;">Page 65</p> <p>1 different and distinct in shape, size,  2 crystallinity and structure, correct?  3 MR. FROST: Objection to  4 form, vague.  5 THE WITNESS: Yeah, when you  6 say grades of talc, I'm a -- I'm a  7 little lost there.  8 BY MR. SMITH:  9 Q. Okay. Cosmetic versus  10 industrial. Pharmaceutical versus  11 industrial versus cosmetic. Those are  12 the grades I'm talking about, my  13 definition of grade.  14 Different grades of talc are  15 different and distinct in size, shape,  16 crystallinity and structure; is that  17 correct?  18 MR. FROST: Objection to  19 form.  20 BY MR. SMITH:  21 Q. Or do you know?  22 A. Yeah, I -- in terms of  23 grades of talc, I would assume that's the  24 case, but I don't study grades of talc.</p>

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<p>1 Q. Different types of asbestos 2 are different and distinct in shape, 3 size, crystallinity and structure, 4 correct? 5 A. That's correct. 6 Q. These characteristics may 7 affect the mineral's reactivity to human 8 cells and carcinogenic potency; is that 9 correct? 10 A. That's correct. 11 Q. The type of asbestos and 12 where it's mined, its shape and size all 13 factor in how it reacts to cells; is that 14 correct? 15 A. Yes. 16 Q. And would the same be of 17 different grades of talc, or do you know? 18 MR. FROST: Objection to 19 form. 20 THE WITNESS: I'd have to 21 study the talc to -- at different 22 grades, and I'm not sure how 23 that's separated out. 24 BY MR. SMITH:</p>	<p>1 good, I'm getting ready to roll to 2 a different section. But I'm good 3 or whatever. Just so long -- 4 THE WITNESS: I'm fine. 5 MR. FROST: I think we can 6 keep going. 7 MR. SMITH: Okay. Okay. 8 All right. Fine. 9 BY MR. SMITH: 10 Q. I want to talk to you about 11 some of your experience, Doctor, as an 12 expert. 13 You said you -- you partly 14 retired since 2014. But you've been 15 testifying in litigation since 2014; is 16 that correct? 17 A. That's correct. 18 Q. And approximately 50 to 19 75 percent of your professional time is 20 spent on litigation since 2014; is that 21 correct? 22 A. That's correct. 23 Q. And would this be the vast 24 majority of your current income since</p>
Page 67	Page 69
<p>1 Q. And just so we're clear, 2 you've never studied cosmetic-grade talc; 3 is that right? 4 MR. FROST: Objection. If 5 she -- if she knows. 6 THE WITNESS: I've studied 7 industrial talcs. 8 BY MR. SMITH: 9 Q. So you've never studied 10 cosmetic-grade talc; is that correct? 11 A. I have not studied cosmetic 12 talcs as I know it. 13 Q. Do you understand that 14 cosmetic talc is what's in Baby Powder 15 and Shower to Shower, which are the 16 products at issue in this case? 17 A. Yes, I do. 18 Q. Okay. I want to talk to you 19 about your -- 20 MR. SMITH: Do you want to 21 take a break for a minute, for a 22 second? 23 MR. FROST: Do you want to? 24 MR. SMITH: I mean, I'm</p>	<p>1 2014, and that being as an expert 2 witness? 3 A. Yes, sir. 4 Q. I noticed from your prior 5 testimony that you attached to your 6 report that you've testified 65 times for 7 defendants in talc litigation over the 8 past four years; is that correct? 9 A. That includes depositions 10 and trials in some of the same matters, 11 yes. 12 Q. You were an employee of 13 Biomedical and Environmental Consultants 14 in 1998; is that right? 15 A. 1998? No. 16 Q. Do I have the date wrong? I 17 might have -- I might have written that 18 down wrong. 19 A. That was 30 years ago. 20 Q. What dates were you at 21 Biomedical and Environmental Consultants? 22 A. I worked part-time for them 23 for a little less than two years. 1988 24 to perhaps 1990.</p>

18 (Pages 66 to 69)

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<p>1 Q. I apologize, I wrote it down 2 wrong. 3 And you worked there with 4 Alfred Wehner, right? 5 A. I never worked with 6 Dr. Wehner. He was the founder of the 7 group as I understand it. 8 Q. And you also understand that 9 he was also a consultant for Johnson &amp; 10 Johnson in talc issues, correct? 11 MR. FROST: Objection to 12 form. 13 THE WITNESS: No. 14 BY MR. SMITH: 15 Q. You don't know that? 16 A. I know from reading the 17 scientific paper, but I don't know about 18 his relationships with Johnson &amp; Johnson. 19 Q. He served -- excuse me. You 20 served as an expert for the Industrial 21 Minerals Association; is that correct? 22 A. Served as an expert. 23 Q. Expert or consultant for the 24 Industrial Minerals Association.</p>	<p>1 correspondence, we've gone back through 2 in Brower and Leavitt with 3 R.T. Vanderbilt, you weren't 4 corresponding with them and consulting 5 with R.T. Vanderbilt? 6 A. I was not consulting with 7 them. I was -- received an assignment 8 through Dr. Wehner's group for 9 correspondence with these individuals. I 10 can't tell you the specific assignment. 11 It was with someone named 12 John Kelse who was their industrial 13 hygienist. 14 Q. And he was an employee of 15 R.T. Vanderbilt, correct? 16 A. He was an employee, yes. 17 Q. You served as an expert for 18 Cyprus Minerals; is that correct? 19 A. I have in litigation. 20 Q. And you are currently 21 serving as an expert for Johnson &amp; 22 Johnson and have in the past; is that 23 correct? 24 A. I have for a little over a</p>
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<p>1 A. I have reviewed proposals 2 for them, yes. 3 Q. And you've served as an 4 expert or consultant for Luzenac; is that 5 correct? 6 A. Not to my knowledge. As a 7 consultant, no, I don't think I've 8 consulted Luzenac. 9 Q. You weren't corresponding 10 with Imerys and Luzenac employees on the 11 progress report of the Shukla paper along 12 with the IMA? 13 A. Yes. I wasn't a consultant 14 for them. I was a recipient of a small 15 grant from something called EUROTALC that 16 may have included Luzenac and other 17 companies for a brief period of time in 18 about 2005. 19 Q. And you've served as an 20 expert or consultant for R.T. Vanderbilt, 21 right? 22 A. No. I never had a formal 23 arrangement with R.T. Vanderbilt. 24 Q. There's plenty of</p>	<p>1 year now, yes. 2 Q. You served as an expert on a 3 scientific advisory board for Owens 4 Corning in the defense of asbestos 5 litigation in the 1980s and 1990s; is 6 that correct? 7 A. That's incorrect. I 8 served -- I went to one meeting there in 9 19 -- in the 1980s, and one in the 1990s, 10 neither of which concerned Owens Corning 11 and litigation. 12 Q. Can you go to Page 45 of the 13 Brower testimony, please. 14 Question, Line 1, on Page 15 45. 16 "Okay. Well, you've 17 consulted with or served as an expert for 18 companies that produce or sold 19 asbestos-containing products, correct: 20 "Answer: Could you be more 21 explicit? 22 "I need to be more explicit 23 than whether you served as an expert or 24 consulted with companies that produced</p>

19 (Pages 70 to 73)

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<p>1 products that contained asbestos? 2 "Answer: The only company 3 that I had a relationship with, and it 4 wasn't a long-standing relationship, was 5 that I agreed to be on the scientific 6 advisory board, I think, once in the 7 1980s and once in the 1990s, with other 8 scientists and review inhouse research by 9 Owens Corning." 10 Is that testimony true? 11 A. Yes. That's what I just 12 stated. 13 Q. Okay. Thank you. 14 You also served as an expert 15 for the tobacco industry in the 1980s; is 16 that correct? 17 MR. FROST: Objection to 18 form. 19 THE WITNESS: I had one 20 assignment, approximately 30 years 21 ago, through Dr. Wehners' company. 22 BY MR. SMITH: 23 Q. And since 2014 you have -- 24 was the answer to my question yes?</p>	<p>1 much are you -- what are you billing for 2 your time here today? 3 A. \$550 an hour. 4 Q. Is that the same billing 5 rate that you would have for trial, 6 deposition? Do you differentiate? 7 A. Yes. It would be the same 8 rate. 9 Q. When is the next time that 10 you're scheduled to testify at trial? 11 A. I'm testifying in the Olson 12 trial in New York at the latter part of 13 this week. 14 Q. What about after that? 15 MR. FROST: Objection. 16 THE WITNESS: I don't have 17 any trial dates on my calendar. 18 BY MR. SMITH: 19 Q. Earlier we had talked about, 20 you talked about your work with the 21 tobacco industry. I want to attach as an 22 exhibit, which is Exhibit -- I'll hand 23 you a copy, Doctor. 24 (Document marked for</p>
Page 75	Page 77
<p>1 A. You'll have to state it 2 again, sir. 3 Q. You have served as an expert 4 and consultant for the tobacco industry 5 in the 1980s; is that correct? 6 MR. FROST: Same objection. 7 THE WITNESS: Yeah I had one 8 assignment where I did a 9 literature search for a lawyer 10 representing the tobacco industry. 11 BY MR. SMITH: 12 Q. Since 2014, you have served 13 as an expert on behalf of companies that 14 manufacture and sell talc-based products; 15 is that correct? 16 A. That's correct. 17 Q. And that will continue today 18 and into the foreseeable future; is that 19 correct? 20 MR. FROST: Objection to 21 form. 22 THE WITNESS: Yes. 23 BY MR. SMITH: 24 Q. I forgot to ask you. How</p>	<p>1 identification as Exhibit 2 Mossman-5.) 3 BY MR. SMITH: 4 Q. I'll attach this as 5 Exhibit 5. This is a January 12, 1990, 6 letter to Mr. Junius McElveen, Esquire. 7 It looks like it's from you. And it's cc 8 to Alfred Wehner. 9 Are you familiar with this 10 document? 11 A. I am. 12 Q. At the beginning you say, 13 "Dear Mr. McElveen, you requested our 14 meeting last week that Mr. Nims" -- "a 15 brief summary of" -- excuse me. "You 16 requested at our meeting last week with 17 Mr. Nims a brief summary of my literature 18 search to date on cellular and molecular 19 mechanisms of carcinogenesis. 20 "I specifically looked for 21 recent research data to substantiate the 22 premise that cigarette smoking prior to 23 1966 would not be sufficient for lung 24 tumor promotion and progression necessary</p>

20 (Pages 74 to 77)



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<p>1 events in the development of tumors 2 during their relatively long latency 3 period in man." 4 Is that what you were -- was 5 that -- that was the task that you were 6 doing? 7 A. The task that I was doing 8 was to do a search on the molecular 9 biology of lung cancers. 10 Q. And the statement that I 11 just read, is that correct? Is that what 12 your task was? Is that what you were 13 doing? 14 A. I'm not sure what cigarette 15 smoking prior to 1966 was relevant to, 16 but I think the question he was asking me 17 were, do components of cigarette smoke 18 have properties that start or influence 19 the development of cancers. 20 Q. And -- but this is your -- 21 you wrote this letter, correct? 22 A. I did. 23 Q. Okay. And on the last 24 paragraph of the letter, before your</p>	<p>1 Owens Corning Fiberglass Corporation, 2 Granville technical center, Granville, 3 Ohio. 4 And it says, "Dear John." 5 And you understand, as you reference in 6 this, that -- that Owens Corning was 7 producing asbestos-containing materials; 8 is that correct? 9 A. No, not at this time point. 10 I was never aware of this in the 1980s. 11 Q. So when you write in the 12 paragraph, final paragraph, "Please find 13 enclosed a brief critique of the recent 14 PNAS covered in the New York Times. I 15 cannot help but surmise that Dr. Selikoff 16 was responsible for the press release. 17 Regardless, the possibility that asbestos 18 binds and introduces malignant and 19 foreign DNA into normal cells of the lung 20 seems highly unlikely." 21 You didn't understand that 22 the issue of asbestos and Owens Corning 23 was relevant to the company? 24 A. No. Dr. Hadley was a</p>
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<p>1 signature, it says, "I will continue to 2 survey new journals in the field as well 3 as Index Medica searches on 'genes and 4 lung cancer.' Please let me know when 5 you would like to meet again for an 6 update." 7 And then did you continue to 8 do what you said you would do? 9 A. No. I wrote a final report 10 after meeting these individuals and no 11 longer was a consultant for Biomedical 12 and Environmental Consulting. 13 Q. I'm going to attach what is 14 Exhibit 6 to the deposition another 15 letter from you. And we talked about 16 Owens Corning just a minute ago. Do you 17 recall that, Doctor? 18 A. Yes. 19 (Document marked for 20 identification as Exhibit 21 Mossman-6.) 22 BY MR. SMITH: 23 Q. And here is a letter from 24 you to Owens Corning. Dr. John Hadley,</p>	<p>1 colleague that I met at a scientific 2 meeting. He was responsible for the 3 development of fiberglasses at their 4 technical center. 5 He was also a scientist who 6 attended meetings on asbestos and was 7 interested in the effects of asbestos on 8 cells -- 9 Q. Did you come -- 10 A. -- by training. 11 Q. I'm sorry. I didn't mean to 12 cut you off. 13 A. I'm sorry. By training, 14 John was someone I actually met when he 15 was getting his degree earlier at Duke 16 University. 17 Q. Did you come to learn that 18 as -- Owens Corning produced 19 asbestos-containing products? 20 A. I came to learn that after I 21 heard about their bankruptcy. I was 22 never aware of that directly. 23 Q. You were a member of the 24 TASSC, weren't you?</p>

21 (Pages 78 to 81)

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<p>1 A. TASSC?</p> <p>2 Q. Mm-hmm.</p> <p>3 A. I don't know what that is,</p> <p>4 and I don't think I've ever paid</p> <p>5 membership dues or I would remember.</p> <p>6 MR. SMITH: Can you hand</p> <p>7 that to the witness.</p> <p>8 (Document marked for</p> <p>9 identification as Exhibit</p> <p>10 Mossman-7.)</p> <p>11 BY MR. SMITH:</p> <p>12 Q. I'm going to attach a</p> <p>13 partial listing of key scientists and --</p> <p>14 I don't know if I can pronounce this --</p> <p>15 academicians supporting the advancement</p> <p>16 of sound science coalition. You don't</p> <p>17 recall this? TASSC?</p> <p>18 A. No, I don't think -- I'm</p> <p>19 just looking at some of the people here,</p> <p>20 who are -- include scientists from</p> <p>21 different spheres including Bruce Ames.</p> <p>22 So no, I am not aware that this is a</p> <p>23 society that I ever joined, no.</p> <p>24 Q. So if you go -- and it's in</p>	<p>1 this is an article entitled,</p> <p>2 "Constructing 'Sound Science' and 'Good</p> <p>3 Epidemiology': Tobacco, Lawyers and</p> <p>4 Public" -- "and the Public Relations</p> <p>5 Firms."</p> <p>6 And it's an article in the</p> <p>7 American Journal of Public Health from</p> <p>8 November of 2001. It's a peer-reviewed</p> <p>9 article. And it's by lead author Ong.</p> <p>10 And it goes down, and if you</p> <p>11 look on the front page, Doctor, it says,</p> <p>12 "Philip Morris' 'Sound Science'</p> <p>13 organization in the United States"?</p> <p>14 Says, "PM," Philip Morris,</p> <p>15 "began its 'sound science' program in</p> <p>16 1993 to stimulate criticism of the 1992</p> <p>17 U.S. Environmental Protection Agency</p> <p>18 (EPA) report, which identified secondhand</p> <p>19 smoke as a Group A human carcinogen.</p> <p>20 Ellen Merlo (vice president, PM Corporate</p> <p>21 Affairs) wrote to William Campbell</p> <p>22 (chairman at PM" -- or Philip Morris --</p> <p>23 "USA)."</p> <p>24 Then it goes on to the -- go</p>
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<p>1 alphabetical order. And on Page 9,</p> <p>2 looking at the top, there's your name.</p> <p>3 Dr. Brooke T. Mossman, professor of</p> <p>4 pathology, College of Medicine,</p> <p>5 University of Vermont, Burlington,</p> <p>6 Vermont. Is that you?</p> <p>7 A. That's me.</p> <p>8 Q. And you are listed on the</p> <p>9 partial listing of key scientists and</p> <p>10 academicians -- butchering that name --</p> <p>11 supporting the advancement of sound</p> <p>12 science coalition, TASSC. Do you see</p> <p>13 that, Doctor?</p> <p>14 A. Yes, I have no idea what</p> <p>15 that is. Sorry.</p> <p>16 Q. Well, maybe we can put some</p> <p>17 context to it here today.</p> <p>18 MR. SMITH: Thank you.</p> <p>19 (Document marked for</p> <p>20 identification as Exhibit</p> <p>21 Mossman-8.)</p> <p>22 BY MR. SMITH:</p> <p>23 Q. I'm going to attach the next</p> <p>24 numbered exhibit which is Number 8. And</p>	<p>1 to the right paragraph, "In February of</p> <p>2 1993, Philip Morris, PM, and its public</p> <p>3 relations firm, APCO Associates, worked</p> <p>4 to launch a 'sound science' coalition in</p> <p>5 the United States with approximately</p> <p>6 320,000 budgeted for the first 24 weeks.</p> <p>7 Three months later, The Advancement For</p> <p>8 Sound Science Coalition, or TASSC, has</p> <p>9 been formed. TASSC described itself as a</p> <p>10 'a not-for-profit coalition advocating</p> <p>11 the use of sound science in public policy</p> <p>12 decisionmaking' even though APCO created</p> <p>13 it to help Philip Morris fight smoking</p> <p>14 restrictions. TASSC's public positioning</p> <p>15 and media campaign were designed to</p> <p>16 minimize its connections with the tobacco</p> <p>17 industry. TASSC's member survey</p> <p>18 mentioned only secondhand smoke among a</p> <p>19 list of other potential examples of</p> <p>20 'unsound, incomplete or unsubstantiated</p> <p>21 science.'"</p> <p>22</p> <p>23 Were you familiar with all</p> <p>24 of this, Doctor, and have you seen this</p>

22 (Pages 82 to 85)

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<p>1 article before?</p> <p>2 A. I haven't seen the article,</p> <p>3 but let me emphasize that I've never been</p> <p>4 a member by consent of TASSC, and there's</p> <p>5 no reason that tobacco would have wanted</p> <p>6 me to be a member, as all my publications</p> <p>7 list tobacco smoke as the Number 1 cause</p> <p>8 of lung disease or lung cancers.</p> <p>9 Q. Well, you -- you haven't</p> <p>10 published any articles on secondhand</p> <p>11 smoke, have you?</p> <p>12 MR. FROST: Objection, form.</p> <p>13 BY MR. SMITH:</p> <p>14 Q. Have you?</p> <p>15 A. Secondhand smoke, no.</p> <p>16 Q. Okay. You mentioned all of</p> <p>17 your research as best -- you mentioned</p> <p>18 all of your research on asbestos, talc</p> <p>19 and cleavage fragments have been</p> <p>20 published and peer-reviewed, high-impact</p> <p>21 scientific journals prior to the event --</p> <p>22 advent of your participation in talc</p> <p>23 litigation in 2014. And that's listed in</p> <p>24 your report.</p>	<p>1 A. When you say -- when you say</p> <p>2 it would --</p> <p>3 Q. Your research being</p> <p>4 published in peer-reviewed high-impact</p> <p>5 scientific journals on asbestos, asbestos</p> <p>6 fibers, talc and cleavage fragments.</p> <p>7 A. Let me emphasize that I'm</p> <p>8 not doing original research anymore on</p> <p>9 talc or asbestos fibers. So that</p> <p>10 statement would not be relevant.</p> <p>11 Q. Okay. Fair enough. I want</p> <p>12 to look at your CV for a second.</p> <p>13 A. Okay.</p> <p>14 Q. And I've got an extra copy</p> <p>15 for you. Several actually.</p> <p>16 MR. FROST: Is this the CV</p> <p>17 that was attached to the report?</p> <p>18 MR. SMITH: It is.</p> <p>19 (Document marked for</p> <p>20 identification as Exhibit</p> <p>21 Mossman-9.)</p> <p>22 BY MR. SMITH:</p> <p>23 Q. All right. Now, you've</p> <p>24 got -- do you have your CV in front of</p>
Page 87	Page 89
<p>1 Do you recall saying that?</p> <p>2 A. Yes.</p> <p>3 Q. I'll assume that would mean</p> <p>4 that that would be the same after your</p> <p>5 involvement in talc litigation. Would</p> <p>6 that be correct?</p> <p>7 A. I'm not sure what you're</p> <p>8 asking.</p> <p>9 Q. Let me rephrase. Let me</p> <p>10 rephrase it.</p> <p>11 A. Okay.</p> <p>12 Q. That was confusing.</p> <p>13 You -- in your report you</p> <p>14 mentioned that your research on asbestos</p> <p>15 fibers, talc, and cleavage fragments have</p> <p>16 been published and peer-reviewed</p> <p>17 high-impact scientific journals prior to</p> <p>18 the advent of your participation in talc</p> <p>19 litigation in 2014?</p> <p>20 A. Yes.</p> <p>21 Q. You agreed with that.</p> <p>22 And I would assume that</p> <p>23 would be the same after your involvement</p> <p>24 post 2014; is that correct?</p>	<p>1 you, Doctor?</p> <p>2 A. I do.</p> <p>3 Q. Okay. And I would like to</p> <p>4 go to Page 15.</p> <p>5 MR. SMITH: I'm going to</p> <p>6 attach this as the next numbered</p> <p>7 exhibit. It's Number 9.</p> <p>8 BY MR. SMITH:</p> <p>9 Q. It says -- it should be</p> <p>10 referred. It says refereed. Is that --</p> <p>11 should it be referred manuscripts?</p> <p>12 A. No.</p> <p>13 Q. Is that -- am I missing</p> <p>14 something?</p> <p>15 A. No, it's refereed.</p> <p>16 Q. Well, then I -- I'm learning</p> <p>17 something new everyday.</p> <p>18 Manuscripts, book chapters,</p> <p>19 monographs and editorials, in parentheses</p> <p>20 peer reviewed.</p> <p>21 A. Correct.</p> <p>22 Q. Hold on. I'm getting ahead</p> <p>23 of myself.</p> <p>24 Let's go back to Page 2.</p>

23 (Pages 86 to 89)



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<p>1 A. Okay.</p> <p>2 Q. And you have reviewer and in</p> <p>3 parentheses journals. And this is all of</p> <p>4 the journals that you have served as a</p> <p>5 reviewer of?</p> <p>6 A. Yes.</p> <p>7 Q. And then if we go to Page 3,</p> <p>8 and you look at that section, it's the</p> <p>9 fourth from the bottom, Regulatory</p> <p>10 Pharmacology and Toxicology. You served</p> <p>11 as a reviewer for that publication; is</p> <p>12 that correct, according to your CV?</p> <p>13 A. Let's see. Could you go to</p> <p>14 the page again?</p> <p>15 Q. Sure. It's Page 3. And if</p> <p>16 you go up, it's under -- like at the top,</p> <p>17 it's got the list of journals, and if you</p> <p>18 see science at the bottom, then you see</p> <p>19 scanning electron microscopy, and then --</p> <p>20 A. Yes.</p> <p>21 Q. -- you see risk analysis,</p> <p>22 then you see Regulatory Pharmacology and</p> <p>23 Toxicology.</p> <p>24 Do you see that?</p>	<p>1 (Document marked for</p> <p>2 identification as Exhibit</p> <p>3 Mossman-10.)</p> <p>4 BY MR. SMITH:</p> <p>5 Q. Okay. And you see it's</p> <p>6 written by David Michaels. And if you go</p> <p>7 to the very last page. It says, "David</p> <p>8 Michaels is an epidemiologist and the</p> <p>9 director of the project on scientific</p> <p>10 knowledge and public policy at the George</p> <p>11 Washington University School of Public</p> <p>12 Health and Health Services.</p> <p>13 "During the Clinton</p> <p>14 administration he served as assistant</p> <p>15 secretary of energy for environment,</p> <p>16 safety and health responsible for</p> <p>17 protecting the health and safety of</p> <p>18 workers, neighboring communities, and the</p> <p>19 environment surrounding the nation's</p> <p>20 nuclear weapons facilities. He was the</p> <p>21 architect of the historic initiative that</p> <p>22 'made peace with the past,' compensating</p> <p>23 U.S. nuclear weapons workers for</p> <p>24 illnesses developed while making or</p>
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<p>1 A. Yes, I reviewed for them.</p> <p>2 Q. Okay. And I want to talk</p> <p>3 about the Journal of Regulatory</p> <p>4 Toxicology and Pharmacology for a second.</p> <p>5 Do you believe this is a</p> <p>6 reputable independent journal?</p> <p>7 A. Yes, I believe it is.</p> <p>8 Historically I've heard a lot about it.</p> <p>9 Q. Do you know who David</p> <p>10 Michaels is?</p> <p>11 A. No.</p> <p>12 Q. You served as a peer</p> <p>13 reviewer of him on the NIOSH 62 bulletin.</p> <p>14 You don't know him, that used to work in</p> <p>15 the federal government?</p> <p>16 A. I -- no, the name doesn't</p> <p>17 ring a bell.</p> <p>18 Q. Well, he wrote a book called</p> <p>19 "Doubt is Their Product: How Industry's</p> <p>20 Assault on Science Threatens Your</p> <p>21 Health."</p> <p>22 And I'd like -- do you have</p> <p>23 a copy in front of you, Doctor?</p> <p>24 A. I do.</p>	<p>1 testing atomic weapons.</p> <p>2 "In 2006 Michaels received</p> <p>3 an American Association" -- "received the</p> <p>4 American Association For the Advancement</p> <p>5 of Science" -- "Sciences, Scientific</p> <p>6 Freedom and Responsibility Award. He</p> <p>7 lives in Bethesda, Maryland."</p> <p>8 And that doesn't ring any</p> <p>9 bells?</p> <p>10 A. No, I don't recognize him</p> <p>11 and I don't recognize the name.</p> <p>12 Q. If you'll go to -- it's on</p> <p>13 Page -- it's the fourth or fifth page in.</p> <p>14 If you look at the top, it's Page 53.</p> <p>15 And he discusses this</p> <p>16 publication for which he served as a</p> <p>17 reviewer on.</p> <p>18 MR. FROST: Objection.</p> <p>19 BY MR. SMITH:</p> <p>20 Q. Quote down at the bottom,</p> <p>21 "There is now a slew of these captured</p> <p>22 journals. The tobacco industry, for</p> <p>23 example, secretly financed the journal</p> <p>24 Indoor and Billet Environment to promote</p>

24 (Pages 90 to 93)

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<p>1 and position for legal purposes the idea 2 that indoor air pollution was a problem 3 caused not by secondhand smoke but by 4 inadequate ventilation. The best known 5 of these publications is Regulatory 6 Toxicology and Pharmacology, the official 7 mouthpiece of the International Society 8 of Regulatory Toxicology and Pharmacology 9 or ISRTP, an impressive name, but really 10 just an association dominated by 11 scientists who work for industry trade 12 groups and consulting firms. 13 "The sponsor of the ISRTP 14 include many of the major tobacco, 15 chemical, and drug manufacturing 16 companies. Its leadership consists of 17 corporate and product defense scientists 18 and attorneys along with a small number 19 of government scientists who have 20 apparently bought in or who do not know 21 better. 22 "The immediate past 23 president was Terry Quill, an attorney 24 who became a senior vice president for</p>	<p>1 academic scientists and I'm not 2 sure of the context of this or the 3 years that this covers. 4 Again, I've reviewed for 5 them in the past. I have not been 6 on their editorial board, so I 7 really can't comment on this. 8 BY MR. SMITH: 9 Q. Do you know what the 10 Weinberg Group's involvement has been in 11 talc litigation or defense of talc? 12 MR. FROST: Objection to 13 form. 14 THE WITNESS: No. 15 BY MR. SMITH: 16 Q. I'd like to show you another 17 article. 18 (Document marked for 19 identification as Exhibit 20 Mossman-11.) 21 BY MR. SMITH: 22 Q. Attached as the next 23 numbered exhibit. Attached -- Doubt is 24 Their Product was Exhibit 10. This is</p>
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<p>1 the product defense of" -- excuse me -- 2 "product defense of the Weinberg Group. 3 Quill also has roots in the tobacco wars, 4 but is not a scientific expert. Rather 5 he served as outside counsel to Philip 6 Morris in the secondhand smoke 7 litigation." 8 Have you ever seen that 9 written about Regulatory Toxicology and 10 Pharmacology, the journal that you served 11 as a reviewer of? 12 MR. FROST: I'll say -- 13 first, I'll just object to using 14 what is basically an opinion piece 15 in this case. 16 But you can answer the 17 question, Brooke. 18 THE WITNESS: Yeah, I'm not 19 familiar with what this source is. 20 It looks like a book chapter. 21 Again, Regulatory Toxicology and 22 Pharmacology is -- historically 23 has been a journal that has been 24 well regarded by government and</p>	<p>1 going to be Exhibit 11. 2 This is an article entitled 3 "Special Contributions: Correspondence 4 About Public Ethics and Regulatory 5 Toxicology and Pharmacology." 6 This is -- this is published 7 in a peer-reviewed journal called the 8 International Journal of Occupational and 9 Environmental Health. And it was in 10 November 19, 2002. And I'm going to read 11 from the -- from the top. 12 MR. FROST: Okay. I just 13 want to object to any connotation 14 that this letter is peer-reviewed. 15 BY MR. SMITH: 16 Q. "In this issue, IJOEH is 17 publishing correspondence concerning 18 conflicts of interest, lack of 19 transparency and absence of editorial 20 independence of the journal Regulatory 21 Toxicology and Pharmacology, RTP." 22 That's where you served as a 23 peer reviewer, right? 24 A. I was asked once or twice to</p>

25 (Pages 94 to 97)

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<p style="text-align: right;">Page 98</p> <p>1 review articles for them. I have no idea 2 when this was. And I have no idea who 3 forwarded me the papers for review. 4 Q. Ma'am, I'm just reading from 5 your CV, and you said that you were a 6 reviewer of Regulatory Toxicology and 7 Pharmacology, correct? 8 A. I have reviewed papers for 9 that journal. 10 Q. "Regulatory Toxicology and 11 Pharmacology is the official publication 12 of the industry-funded International 13 Society of Regulatory Toxicology and 14 Pharmacology or IS RTP." Then it goes 15 down into the second -- third paragraph. 16 "IJOEH has chosen to publish this 17 exchange in order to alert readers to the 18 ways in which supposedly credible 19 peer-reviewed journals may be co-opted by 20 corporations seeking to give credibility 21 to particular scientific points of view. 22 "RTP publishes a large 23 number of studies conducted by 24 industry-funded scientists. These</p>	<p style="text-align: right;">Page 100</p> <p>1 Excuse me, ma'am. 2 THE WITNESS: Pardon me? 3 MS. O'DELL: "Object to the 4 form" is the appropriate 5 objection. 6 MR. FROST: I'll try to 7 remember that. 8 BY MR. SMITH: 9 Q. And then I want to go on 10 further. It says, "November 19, 2002, 11 Ms. Kirsten Chrisman, managing editor, 12 Journals Division, Academic Press. And a 13 Paul Weislogel, vice president, global 14 Society, of Elsevier, Science, Inc. Are 15 you familiar with that publication? 16 They publish a lot of 17 scientific literature. 18 A. Who is this now? 19 Q. I might be pronouncing the 20 name -- Elsevier Science, Inc.? 21 A. Yes. I'm looking at the 22 journal, though, sir. And this is a 23 letter, and it's signed by a number of 24 individuals, several whom I recognize as</p>
<p style="text-align: right;">Page 99</p> <p>1 studies later become part of industry's 2 efforts to influence federal regulatory 3 agencies or defend litigation claims 4 concerning toxic exposure. 5 "Without safeguards to 6 assure their independence of the 7 editorial process, suspicion, some of it 8 well deserved, is cast over studies and 9 journals." 10 And that was written by the 11 editor-in-chief of this publication. 12 Do you see that? 13 MR. FROST: Again, I object 14 to the use of what is clearly an 15 opinion piece to try to establish 16 facts in this case and in 17 questioning this witness. 18 THE WITNESS: If I can -- 19 MS. O'DELL: "Object to the 20 form" -- 21 THE WITNESS: If I can look 22 at the -- 23 MS. O'DELL: -- is the 24 appropriate objection.</p>	<p style="text-align: right;">Page 101</p> <p>1 plaintiff experts. 2 Q. Ma'am, there's not a 3 question on the table. I'm going to ask 4 you a question though. Okay. 5 MR. FROST: Well, I think 6 you did ask a question. 7 THE WITNESS: Well, I think 8 you asked me to look at this, and 9 I would give this, based upon the 10 signatures here, that this is not 11 a peer-reviewed letter. And that 12 it's not relevant. It looks like 13 a letter that was written. It 14 certainly was not peer-reviewed 15 and again, I want to emphasize 16 that this publication that you're 17 questioning is the official 18 publication of a society of which 19 I am not a member. 20 BY MR. SMITH: 21 Q. Ma'am, do we need to go back 22 to your CV again where you were listed as 23 a peer reviewer of this publication? 24 A. I did not review this</p>

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<p style="text-align: right;">Page 102</p> <p>1 publication.</p> <p>2 Q. You're not a -- you're not a</p> <p>3 peer reviewer of Regulatory Toxicology</p> <p>4 and Pharmacology?</p> <p>5 A. I, in the past, through</p> <p>6 perhaps 40 years, have reviewed papers</p> <p>7 for them.</p> <p>8 Q. And that's the extent --</p> <p>9 A. It could have been one or --</p> <p>10 Q. That's your extent of</p> <p>11 involvement with Regulatory Toxicology</p> <p>12 and Pharmacology?</p> <p>13 A. I have never been on their</p> <p>14 editorial board, and I know little about</p> <p>15 the journal. I'm not a member of the</p> <p>16 society of -- that disseminates this</p> <p>17 journal.</p> <p>18 Q. I'm going to read the</p> <p>19 document, "Dear Ms. Chrisman and Mr.</p> <p>20 Weislogel, we write you to express our</p> <p>21 concerns about apparent conflicts of</p> <p>22 interest, lack of transparency, and the</p> <p>23 absence of editorial independence of the</p> <p>24 Journal of Regulatory Toxicology and</p>	<p style="text-align: right;">Page 104</p> <p>1 trade association that have direct</p> <p>2 incentive to minimize the regulatory</p> <p>3 burden on industry, Bullet Point 2.</p> <p>4 "A significant percentage of</p> <p>5 members of the RTP editorial board have</p> <p>6 financial ties to companies whose</p> <p>7 products or byproducts are the subject of</p> <p>8 studies published by the RTP."</p> <p>9 Next, down at the bottom of</p> <p>10 Page 387, "RTP editorial's commonly</p> <p>11 support industry, antiregulatory goals."</p> <p>12 Next bullet point: "RTP</p> <p>13 serves as a convenient venue for</p> <p>14 publication of industry research and</p> <p>15 gives the credibility of a peer-reviewed</p> <p>16 journal to articles that may not have</p> <p>17 been subjected to full and meaningful</p> <p>18 independent review."</p> <p>19 Next bullet point: "RTP</p> <p>20 routinely fails to disclose relevant</p> <p>21 conflicts of interest."</p> <p>22 Then it goes on to the next</p> <p>23 section. "Given the considerable</p> <p>24 industry support received by ISRTP, RTP's</p>
<p style="text-align: right;">Page 103</p> <p>1 Pharmacology, RTP, which you publish.</p> <p>2 "As you know, that journal</p> <p>3 is the official publication of the</p> <p>4 International Society of Regulatory</p> <p>5 Toxicology and Pharmacology or ISRTP.</p> <p>6 Our concerns about Regulatory Toxicology</p> <p>7 and Pharmacology include:"</p> <p>8 Bullet point, "The journal's</p> <p>9 apparent bias in favor of industries that</p> <p>10 are subject to governmental health and</p> <p>11 environmental regulations that provide</p> <p>12 financial support to RTP's sponsor,</p> <p>13 ISRTP.</p> <p>14 "ISRTP is supported by,</p> <p>15 among others, the American Chemical</p> <p>16 Council" -- "Chemistry Council,</p> <p>17 Bristol-Myers Squibb Company, Dow</p> <p>18 AgroSciences, Eastman Kodak, Gillette</p> <p>19 Company, In-Spec Chemical Corporation.</p> <p>20 Merck &amp; Co., Inc., Procter &amp; Gamble,</p> <p>21 R.J. Reynolds Tobacco Company, The</p> <p>22 Sapphire Group, Inc., Schering-Plough</p> <p>23 Research Institute, and SmithKline</p> <p>24 Beecham Pharmaceuticals, all companies or</p>	<p style="text-align: right;">Page 105</p> <p>1 industry oriented editorial board, the</p> <p>2 too-frequent antiregulatory tenor of</p> <p>3 RTP's editorials, and the preponderance</p> <p>4 of publications by industry-funded</p> <p>5 scientists, we urge Academic</p> <p>6 Press/Elsevier to" -- I'm mispronouncing</p> <p>7 that name -- "to increase the credibility</p> <p>8 of the journal by insisting that RTP, (1)</p> <p>9 sever its ties to the industry-sponsored</p> <p>10 ISRTP; (2) reconstitute its advisory</p> <p>11 board to dramatically reduce the</p> <p>12 influence of industry scientists,</p> <p>13 industry lawyers, and academic</p> <p>14 consultants to industry; and (3) adopt an</p> <p>15 editorial policy about conflicts of</p> <p>16 interest."</p> <p>17 And then at the end of</p> <p>18 the -- of this letter in this</p> <p>19 peer-reviewed journal, it has signed by</p> <p>20 one -- let's see. One, two, three, four</p> <p>21 -- 32, excuse me, that's another page.</p> <p>22 It goes onto the next page.</p> <p>23 42 different Ph.D.s,</p> <p>24 doctors, of all walks through the United</p>

27 (Pages 102 to 105)

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<p>1 States and around the world, from 2 different institutions, different 3 hospitals -- do you see that, Doctor? 4 MR. FROST: I'm going to 5 object. Wonderful testimony you 6 just gave. 7 Again I'm going to object to 8 the use of an opinion piece. I'll 9 object to just reading from 10 something that, first off is -- 11 MR. SMITH: Just state your 12 objection. I don't need a 13 speaking objection. 14 MR. FROST: -- second -- 15 MR. SMITH: I don't need a 16 speaking objection. 17 MR. FROST: But I think this 18 entire line of questioning, quite 19 frankly, is completely improper. 20 And as Dr. Mossman said, 21 she's never seen this before. And 22 we've already established that 23 this is just an opinion piece 24 that's signed on by several</p>	<p>1 do we have a Special Master in 2 this case? 3 MS. O'DELL: Yes. 4 MR. SMITH: All right. So 5 I've warned you, I've done it 6 twice now. I mean -- okay. All 7 right. 8 BY MR. SMITH: 9 Q. Have you seen this piece, 10 Doctor? 11 A. I have not. And I'm not a 12 member of the editorial board of this 13 journal. And these individuals, as I 14 point out, are people who -- many of whom 15 are involved as plaintiff expert 16 witnesses in litigation. And that I do 17 recognize. 18 Q. Okay. 19 A. I would also -- 20 Q. I know you said -- I'm 21 sorry? 22 A. I -- I also want to bring up 23 the point that International Journal of 24 Occupational and Environmental Health,</p>
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<p>1 plaintiffs' attorneys. Answer 2 your question -- 3 MR. SMITH: Look, I'm going 4 to let -- I'm going to let you go. 5 There are no more speaking 6 objections; otherwise, I'm going 7 to get the Court on the phone. 8 You can speak -- you can voice 9 your objection, but we're not 10 going to have speaking objections. 11 MR. FROST: Well, we'll see. 12 I mean, I've -- as I've said, I 13 just -- I'm objecting to the 14 proprietary of even using, you 15 know, this example. 16 Just sitting there and 17 reading a -- a letter into the 18 record and not asking a question 19 about it, is not the proper -- 20 MR. SMITH: I'll get the 21 Court involved. If you're going 22 to continue to speak, do speaking 23 objections, I'm going to call -- 24 I -- we have a Special Master --</p>	<p>1 I'm not sure that journal still exists. 2 If this is the one, as the letter is 3 signed, that Dr. Egilman was editor of 4 this journal, has been dropped by 5 Elsevier. 6 Q. Well, let's talk about a 7 few -- a few studies. Did you publish a 8 publication called "Assessment of the 9 pathogenic potential of asbestiform 10 versus non-asbestiform particulates 11 (cleavage fragments) in in vitro (cell or 12 organ culture) models and bioassays"? 13 A. Yes. I -- that was the 14 paper that I published in this journal. 15 Q. And, in fact, it was 16 published in the Regulatory Toxicology 17 and Pharmacology publication that we just 18 went over all this? 19 MR. FROST: Form. 20 THE WITNESS: I just said 21 that. 22 BY MR. SMITH: 23 Q. You just told me earlier 24 that your only involvement with this</p>

28 (Pages 106 to 109)



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<p>1 publication was looking at two 2 peer-reviewed articles. You didn't state 3 anything about actually publishing on the 4 assessment of the pathogenic potential of 5 asbestiform versus cleavage fragments. 6 You didn't state that earlier when you -- 7 when you talked about your review -- 8 A. Sir -- 9 Q. -- your time -- excuse me. 10 As your time as a reviewer for this 11 publication, did you? 12 MR. FROST: Objection to 13 form. 14 THE WITNESS: You -- you did 15 not ask me if I published in this 16 journal. 17 Yes, I have an article 18 published in this journal. 19 (Document marked for 20 identification as Exhibit 21 Mossman-12.) 22 BY MR. SMITH: 23 Q. Well, ma'am, you told me, 24 and I can have them read it back to you,</p>	<p>1 Q. Well, let's -- let's look at 2 it. Your conclusions of assessing 3 whether -- of the pathogenic potential of 4 asbestos versus non-asbestiform cleavage 5 fragments. We look at the abstract, and 6 in the last sentence, "The available 7 studies show that cleavage fragments are 8 less bioreactive and cytotoxic than 9 asbestiform fibers." 10 Was that your conclusion? 11 A. That is the conclusion based 12 upon all my peer-reviewed papers that 13 have been published on this topic. Yes. 14 This is a review. 15 MR. SMITH: I'll attach that 16 as Exhibit 12. 17 BY MR. SMITH: 18 Q. And on your reference 19 materials that you have for this case 20 that I received, you have an article by 21 Alfred Wehner. "Cosmetic Talc Should Not 22 Be Listed As a Carcinogen: Comments on 23 NTP Deliberations to Talc As a 24 Carcinogen."</p>
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<p>1 that the only involvement you had with 2 this publication was reviewing two 3 articles. Do we need to go back to the 4 testimony? 5 MR. FROST: Objection to 6 form. 7 THE WITNESS: I'm sorry, 8 sir, but you were asking me about 9 Page 3 on my CV, which lists 10 journals that I have reviewed for. 11 And the questions that you 12 asked me I answered with regard to 13 my editorial responsibility in 14 reviewing a paper or two for this 15 journal. 16 BY MR. SMITH: 17 Q. You left out that you 18 actually published in the journal too? 19 MR. FROST: Objection to 20 form. 21 THE WITNESS: I -- I 22 acknowledge that I published in 23 the journal. 24 BY MR. SMITH:</p>	<p>1 Do you recall that? 2 A. I do. 3 Q. You also listed a paper by 4 Mr. Zazenski, who -- it's entitled "Talc: 5 Occurrence, Characterization and Consumer 6 Applications." 7 Do you see that? Do you 8 recall that? 9 A. Yes. 10 Q. Okay. Did you know both of 11 those were published in Regulatory 12 Toxicology and Pharmacology? 13 A. I don't recall that. But -- 14 Q. Let's look at them. 15 MR. FROST: Which one? Are 16 you going to mark this? 17 MR. SMITH: I'm going to 18 mark Alfred Wehner's publication 19 as Exhibit 13. And Zazenski as 20 14. 21 (Document marked for 22 identification as Exhibit 23 Mossman-13.) 24 (Document marked for</p>

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<p>1 identification as Exhibit 2 Mossman-14.) 3 BY MR. SMITH: 4 Q. And let's look at both of 5 these. So, we have -- we went over 6 Regulatory Toxicology and Pharmacology, 7 what David Michaels wrote about them, 8 what was in the International Journal of 9 Occupational and Environmental Health 10 that you had not seen before. We went 11 over your publication in that journal, 12 which we just talked about and discussed 13 your opinion in the abstract that when 14 looking at asbestos versus the cleavage 15 fragments, you concluded the available 16 studies showed that cleavage fragments 17 are less bioreactive and cytotoxic than 18 asbestiform fibers. 19 Now we'll move to 20 Dr. Wehner's assessment in the same 21 journal. And if you look down at his 22 conclusion in the abstract, "Considering 23 talc as a carcinogen lacks convincing 24 scientific documentation."</p>	<p>1 consumers." And then he quotes Alfred 2 Wehner. 3 Do you see that? 4 MR. FROST: Objection to 5 form. 6 THE WITNESS: Yeah, you're 7 going a little fast here. Could 8 you just point me to where you're 9 reading from? 10 BY MR. SMITH: 11 Q. Sure. It's under -- it's 12 Page 11 of 12 under the conclusions. 13 A. Okay. Yeah. 14 Q. Do you see that? 15 A. Yes. 16 MR. SMITH: Do you want to 17 take a break, or do you want to go 18 on to a different section? 19 MR. FROST: If you're going 20 to move on to another section, 21 I'll use the restroom. 22 THE VIDEOGRAPHER: Off the 23 record. Time is 10:36. 24 (Short break.)</p>
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<p>1 Do you see that? 2 MR. FROST: Objection to 3 form, the beginning of that 4 question. 5 BY MR. SMITH: 6 Q. Do you see that, Doctor? 7 A. I see it in the abstract, 8 yes. 9 Q. And then if we go -- that's 10 in Exhibit 13. 11 And if we go to Exhibit 14, 12 "Talc Occurrence, Characterization, and 13 Consumer Applications," and we go to what 14 Mr. Zazenski wrote in this publication, 15 also published in Regulatory Toxicology 16 and Pharmacology, his conclusion on Page 17 11 of 12. "Used for decades in a wide 18 variety of cosmetic and other 19 applications, talc has proven to be the 20 safest among all consumer products. 21 "A thorough review of the 22 literature provides no convincing 23 evidence that cosmetic talc when used as 24 intended presents any health risk to</p>	<p>1 THE VIDEOGRAPHER: We are 2 going back on record. Beginning 3 Media File Number 2. The time is 4 10:47. 5 BY MR. SMITH: 6 Q. Okay. Doctor, what are the 7 different histological types of ovarian 8 cancer? 9 A. There are four types. There 10 is invasive, the serous, which is the 11 most common, high grade, endometrioid, 12 clear cell, and mucinous. 13 Q. Do you know which type is 14 diagnosed most in the United States? 15 A. Yes. The first category of 16 the serous. 17 Q. Where do most experts 18 believe the histological type originates 19 in the human body? 20 MR. FROST: Objection to 21 form. 22 THE WITNESS: They don't 23 know. They are all derivatives of 24 epithelioid or epithelial cells.</p>

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<p>1 But it's unclear whether they have</p> <p>2 a common precursor or whether</p> <p>3 there are different precursors</p> <p>4 used for different histotypes.</p> <p>5 BY MR. SMITH:</p> <p>6 Q. I'm talking about --</p> <p>7 specifically about serous. Do you</p> <p>8 understand that the large -- or do you</p> <p>9 understand that the large majority --</p> <p>10 vast majority of epithelial ovarian</p> <p>11 cancers diagnosed in the United States</p> <p>12 are serous type?</p> <p>13 A. Yes.</p> <p>14 Q. And my question to you is,</p> <p>15 do you know where scientists think that</p> <p>16 the serous type histological type of</p> <p>17 epithelial ovarian cancer originates?</p> <p>18 A. If you mean the site, it's</p> <p>19 thought that it originates in the</p> <p>20 fallopian tubes.</p> <p>21 Q. Peritoneal mesothelial cells</p> <p>22 line the peritoneal cavity, fallopian</p> <p>23 tubes, and ovaries of a woman, correct?</p> <p>24 A. They do, yes.</p>	<p>1 a risk factor on that mechanism as well?</p> <p>2 MR. FROST: Objection to</p> <p>3 form.</p> <p>4 THE WITNESS: No. I think</p> <p>5 that that's an open-ended question</p> <p>6 on what the estrogen or the</p> <p>7 incessant ovulation does. I don't</p> <p>8 believe that it's linked to</p> <p>9 chronic inflammation, for example,</p> <p>10 in the ovary or in the fallopian</p> <p>11 tubes.</p> <p>12 BY MR. SMITH:</p> <p>13 Q. Okay.</p> <p>14 A. Or that has not been</p> <p>15 demonstrated.</p> <p>16 Q. In 2010, did IARC list talc</p> <p>17 as a possible carcinogen?</p> <p>18 MR. FROST: Objection to</p> <p>19 form.</p> <p>20 THE WITNESS: Yes. It</p> <p>21 listed talc, yes.</p> <p>22 BY MR. SMITH:</p> <p>23 Q. And IARC in 2012 listed</p> <p>24 asbestos as a known human ovarian</p>
Page 119	Page 121
<p>1 Q. Do you have an opinion about</p> <p>2 what biological mechanisms or pathways</p> <p>3 can lead to ovarian cancer?</p> <p>4 A. I have an idea based upon</p> <p>5 what I have read and that is that there</p> <p>6 are certainly genetic predispositions</p> <p>7 that are associated with it. There</p> <p>8 certainly is an estrogen-dependent effect</p> <p>9 or incessant ovulation, but in terms of</p> <p>10 other causes, they aren't fully</p> <p>11 understood.</p> <p>12 Q. And what about incessant</p> <p>13 ovulation can lead to a woman contracting</p> <p>14 ovarian cancer?</p> <p>15 A. Incessant ovulation is</p> <p>16 thought to be important because it gives</p> <p>17 rise to estrogens that may influence the</p> <p>18 process of tumor development.</p> <p>19 Q. What about the rupture --</p> <p>20 the more than normal or abnormal rupture</p> <p>21 of incessant ovulation of the egg from</p> <p>22 the ovary and causing inflammation and</p> <p>23 injury chronically? Have you not read</p> <p>24 articles that base incessant ovulation as</p>	<p>1 carcinogen, correct?</p> <p>2 MR. FROST: Objection to</p> <p>3 form.</p> <p>4 THE WITNESS: It did.</p> <p>5 BY MR. SMITH:</p> <p>6 Q. And in 2010, in IARC, and on</p> <p>7 Prop 65, asbestiform talc is also a known</p> <p>8 human carcinogen. Are you familiar with</p> <p>9 that?</p> <p>10 A. No. You are going to have</p> <p>11 to refresh my on Prop 65.</p> <p>12 Q. Prop 65 is the</p> <p>13 classification in California. Are you</p> <p>14 familiar with that classification --</p> <p>15 A. I'm not familiar --</p> <p>16 Q. -- of hazardous substance?</p> <p>17 A. -- with the details of Prop</p> <p>18 65.</p> <p>19 Q. Okay.</p> <p>20 (Document marked for</p> <p>21 identification as Exhibit</p> <p>22 Mossman-15.)</p> <p>23 BY MR. SMITH:</p> <p>24 Q. I'm going to attach as</p>



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<p>1 Exhibit 15, which is from OEHHA. It's</p> <p>2 the Prop 65 listing of talc containing</p> <p>3 asbestiform fibers. Have you seen that</p> <p>4 listing, Doctor, before?</p> <p>5 A. I have not.</p> <p>6 Q. Have you seen the IARC</p> <p>7 listing of talc-containing asbestiform</p> <p>8 fibers as a Group 1 carcinogen? Have you</p> <p>9 seen that before?</p> <p>10 A. Have I seen, you mean the</p> <p>11 monograph or --</p> <p>12 (Document marked for</p> <p>13 identification as Exhibit</p> <p>14 Mossman-16.)</p> <p>15 BY MR. SMITH:</p> <p>16 Q. Yes, I'm going to attach</p> <p>17 that as Exhibit 16.</p> <p>18 A. Okay.</p> <p>19 Q. Keep it. Have you seen that</p> <p>20 before?</p> <p>21 MR. FROST: Just for the</p> <p>22 record, because it's just a</p> <p>23 section of it, is this the -- the</p> <p>24 2010 talc monograph?</p>	<p>1 have my expert report in front of</p> <p>2 me.</p> <p>3 BY MR. SMITH:</p> <p>4 Q. In your -- I'm sorry --</p> <p>5 A. Like the jargon -- I'm</p> <p>6 sorry --</p> <p>7 Q. Go ahead.</p> <p>8 A. -- about the causation</p> <p>9 opinion. I -- I list several opinions.</p> <p>10 Q. I understand.</p> <p>11 A. But causation opinions, I'm</p> <p>12 not certain what you mean exactly.</p> <p>13 Q. I never saw a definitive</p> <p>14 opinion in your report that says talc</p> <p>15 does not cause ovarian cancer.</p> <p>16 MR. FROST: Objection to</p> <p>17 form.</p> <p>18 THE WITNESS: It -- it</p> <p>19 should have been conveyed as such.</p> <p>20 BY MR. SMITH:</p> <p>21 Q. Okay. And we'll get to your</p> <p>22 report in a minute.</p> <p>23 A. Okay.</p> <p>24 Q. Well, when did you arrive at</p>
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<p>1 MR. SMITH: Yes. It should</p> <p>2 say it on the --</p> <p>3 MR. FROST: Yeah, it says</p> <p>4 talc on the top, but it's one of</p> <p>5 the --</p> <p>6 MR. SMITH: Yeah.</p> <p>7 BY MR. SMITH:</p> <p>8 Q. Have you seen that before,</p> <p>9 Doctor?</p> <p>10 A. I have read this document,</p> <p>11 yes.</p> <p>12 Q. Okay. I looked at -- are</p> <p>13 all your opinions in this case contained</p> <p>14 in your report?</p> <p>15 A. I believe so. Yes.</p> <p>16 Q. And in your report, you</p> <p>17 don't give a causation opinion on</p> <p>18 cosmetic talc and ovarian cancer, do you?</p> <p>19 MR. FROST: Objection to</p> <p>20 form.</p> <p>21 THE WITNESS: You're --</p> <p>22 you're going to have to tell me</p> <p>23 what the causation opinion is</p> <p>24 specifically compared -- I don't</p>	<p>1 your opinions in this case? I mean I see</p> <p>2 the draft report was February 25, 2019,</p> <p>3 was when it's signed.</p> <p>4 Surely you came to your</p> <p>5 opinions before it was drafted?</p> <p>6 MR. FROST: Form.</p> <p>7 THE WITNESS: I did. I</p> <p>8 reviewed all the literature and</p> <p>9 came to my opinions before I</p> <p>10 drafted that report, which would</p> <p>11 have been probably at the end of</p> <p>12 December or in January of this</p> <p>13 year.</p> <p>14 BY MR. SMITH:</p> <p>15 Q. Okay. So you're saying in</p> <p>16 your opinion, you give an opinion in your</p> <p>17 report that -- on cosmetic-grade talc and</p> <p>18 it causing ovarian cancer, or not causing</p> <p>19 ovarian cancer?</p> <p>20 MR. FROST: Objection to</p> <p>21 form.</p> <p>22 THE WITNESS: Yeah, I'd have</p> <p>23 to look at my opinions.</p> <p>24 BY MR. SMITH:</p>

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<p>1 Q. Hold on a second. Had you 2 formed that opinion in October 26th of 3 2018? 4 A. Which opinion, to answer? 5 Q. That talc, cosmetic-grade 6 talc does not cause ovarian cancer. 7 A. Yes. 8 Q. You weren't able to give me 9 that opinion in the Brower case. I 10 specifically asked you many, many times 11 and your counsel objected saying she does 12 not going to give a causation opinion. 13 She's not here to give a causation 14 opinion. Do you recall that? 15 MR. FROST: Objection to 16 form. 17 THE WITNESS: Yes, that 18 was -- that was before I reviewed 19 the scientific literature. 20 BY MR. SMITH: 21 Q. Well, I just asked you, did 22 you have that opinion on October 26, 2018 23 and you said you did. And that's when 24 you were deposed in Brower.</p>	<p>1 of her opinion that talc does not cause 2 ovarian cancer and I need to get to the 3 bottom of that. 4 He said, "Yeah, I understand 5 that. I'm trying to tell you that -- 6 that not going to ask her as a broad a 7 question as does talc cause ovarian 8 cancer based on all these entities. 9 We're going to ask her about her research 10 and what it means in terms of talc's 11 ability to cause the changes that can 12 lead to cancer, and then specifically the 13 testimony she's given previously 14 regarding her in vitro studies as well as 15 her review of animal studies dealing with 16 mesothelioma and talc, and testimony 17 she's given previously about cleavage 18 fragments, and then finally her opinions 19 and interpretation of Lauren 20 Plunkett's -- let me rephrase that. 21 The -- her comments on the interpretation 22 that Lauren Plunkett provided concerning 23 her studies as well as similar -- similar 24 studies."</p>
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<p>1 MR. FROST: Objection. 2 THE WITNESS: Yeah, I'm not 3 sure what you mean about by my 4 opinion. My opinion has been 5 bolstered in terms of talc and 6 causation by reading since 7 October 18th. 8 BY MR. SMITH: 9 Q. I want to read on Page 66 of 10 the Brower deposition. 11 MR. FROST: Give me a 12 second. Let me catch up to you. 13 THE WITNESS: 66? Okay. 14 MR. FROST: Do you have 15 that, Brooke? 16 THE WITNESS: Hold on. I'm 17 almost there. 18 Okay. 19 BY MR. SMITH: 20 Q. And it goes -- it's 66 and 21 I'm going to go to Line 4. 22 "But that's not what she 23 said and nor has she retracted. There 24 are three things she relies for the basis</p>	<p>1 Has that changed, that 2 you're -- you're going to give an opinion 3 generally that talc does not cause 4 ovarian cancer from what your counsel 5 said you were going to do in October 26, 6 2018? 7 MR. FROST: Objection to 8 form. I just want to make the 9 record clear that Brower is 10 obviously different than the MDL 11 case. 12 MR. SMITH: I understand. 13 MR. FROST: But you can 14 answer. 15 BY MR. SMITH: 16 Q. Is -- is your report and 17 your testimony in this case different 18 than what you just -- what was said here? 19 A. It's not any different. I 20 think the emphasis is different, that I'm 21 relying upon my own research. But in 22 addition, since October 18th -- or 26, 23 2018, I have read the literature in terms 24 of the lack of migration of talc to the</p>

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<p>1 ovary. I've read the epidemiology. And</p> <p>2 I do have an opinion that is based upon</p> <p>3 the peer-reviewed scientific medical</p> <p>4 literature that talc is not associated</p> <p>5 with the causation of ovarian cancers.</p> <p>6 Q. Okay. We'll go specifically</p> <p>7 in your report in a minute. I just</p> <p>8 wanted to bring that question out right</p> <p>9 now.</p> <p>10 You cannot tell me what the</p> <p>11 risk factors for -- of ovarian cancer</p> <p>12 are, can you?</p> <p>13 A. The risk factors vary</p> <p>14 according to the epidemiological studies.</p> <p>15 Q. Do you consider talc a risk</p> <p>16 factor for ovarian cancer?</p> <p>17 MR. FROST: Objection to</p> <p>18 form.</p> <p>19 THE WITNESS: If you are</p> <p>20 talking about a significant, it's</p> <p>21 not a simple yes or no answer.</p> <p>22 I would say that it -- talc</p> <p>23 is not a significant risk factor</p> <p>24 for ovarian cancer.</p>	<p>1 MR. SMITH: I'd like to</p> <p>2 attach this as the next numbered</p> <p>3 Exhibit 17.</p> <p>4 (Document marked for</p> <p>5 identification as Exhibit</p> <p>6 Mossman-17.)</p> <p>7 BY MR. SMITH:</p> <p>8 Q. It's a printout from the</p> <p>9 website, the University of Vermont</p> <p>10 Medical Center on ovarian cancer.</p> <p>11 And if you go to the second</p> <p>12 page, Doctor, it talks -- it has listed</p> <p>13 here the gynecological -- gynecologic</p> <p>14 oncology group with that organization.</p> <p>15 Do you see that on the front page?</p> <p>16 A. Yes. I don't know who -- I</p> <p>17 don't see any names listed.</p> <p>18 Q. And this is -- do you see at</p> <p>19 the top, University of Vermont Medical</p> <p>20 Center? Do you see that?</p> <p>21 A. I do.</p> <p>22 Q. And it has ovarian cancer</p> <p>23 listed at the top, correct, right under</p> <p>24 the heading? Right here.</p>
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<p>1 BY MR. SMITH:</p> <p>2 Q. That wasn't my question,</p> <p>3 Doctor. Is talc a risk factor for</p> <p>4 ovarian cancer?</p> <p>5 MR. FROST: Objection.</p> <p>6 THE WITNESS: I think I just</p> <p>7 answered that, that it's not a</p> <p>8 simple yes or no.</p> <p>9 That the epidemiological</p> <p>10 studies indicate that it is not.</p> <p>11 BY MR. SMITH:</p> <p>12 Q. Are you an epidemiologist?</p> <p>13 A. No, but I certainly read the</p> <p>14 epidemiology.</p> <p>15 Q. So do you consider talc a</p> <p>16 risk factor for ovarian cancer?</p> <p>17 A. No, I don't.</p> <p>18 Q. Okay. You are affiliated</p> <p>19 with the University of Vermont Medical</p> <p>20 Center, aren't you?</p> <p>21 A. I am.</p> <p>22 Q. Is it a reputable</p> <p>23 organization?</p> <p>24 A. Yes.</p>	<p>1 A. Hold on here. Yes.</p> <p>2 Q. And if you flip to the</p> <p>3 second page, "Ovarian cancer, what you</p> <p>4 need to know." It says, "Ovarian cancer,</p> <p>5 what is it? Ovarian cancer risk</p> <p>6 factors." You see, "Age older than 55,</p> <p>7 obesity, reproductive history, family</p> <p>8 history of ovarian cancer, personal</p> <p>9 history of breast cancer, put talcum</p> <p>10 powder directly on genitals or sanitary</p> <p>11 napkins."</p> <p>12 Do you see that?</p> <p>13 MR. FROST: Objection to</p> <p>14 form.</p> <p>15 THE WITNESS: Yeah, where is</p> <p>16 this? I'm sorry. Oh, I see it,</p> <p>17 okay.</p> <p>18 BY MR. SMITH:</p> <p>19 Q. It's the third page. So you</p> <p>20 would disagree with the University of</p> <p>21 Vermont Medical Center on whether talc is</p> <p>22 a risk factor when put directly on the</p> <p>23 genitals and sanitary napkins for ovarian</p> <p>24 cancer?</p>

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<p>1 A. I rely, again, upon the 2 peer-reviewed scientific literature that 3 indicates certainly in cohort studies and 4 case-control studies that it is not a 5 risk factor in ovarian cancer. 6 MR. SMITH: I'm going to 7 object as nonresponsive. 8 BY MR. SMITH: 9 Q. Doctor, do you disagree with 10 the University of Vermont Medical Center 11 in this publication that lists risk 12 factors for ovarian cancer, and one 13 being, "Put talcum powder directly on 14 genitals or sanitary napkins"? 15 MR. FROST: Objection to 16 form. It's not a publication. 17 THE WITNESS: Yeah, and let 18 me emphasize that this isn't a -- 19 MR. SMITH: And I'm -- I've 20 just about had it. The speaking 21 objections are going to stop, or 22 I'm going to get the court in. 23 I'm -- this is the last one. Your 24 speaking objections --</p>	<p>1 disagree with the University of Vermont 2 Medical Center publication that I have in 3 front of you that's Exhibit 17, that 4 lists risk factors for ovarian cancer, 5 one being, "Put talcum powder directly on 6 genitals or sanitary napkins"? Do you 7 agree or disagree with that? 8 MR. FROST: Objection to 9 form. 10 THE WITNESS: I disagree 11 that that is a risk factor that's 12 significant. 13 BY MR. SMITH: 14 Q. Well, hold on. Wonder if 15 it's not significant. Do you believe 16 that talc is a risk -- an insignificant 17 risk factor? 18 A. I -- when you say 19 insignificant, I would -- I -- let me 20 qualify that these studies that I've read 21 in terms of the epidemiology show that it 22 is -- that the risks of talc are not 23 significant. 24 Q. So, there is some risk of</p>
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<p>1 MR. FROST: Sure. I was 2 just -- 3 MR. SMITH: Object to form. 4 MR. FROST: I was just 5 making it clear to you what your 6 objection is so you can -- 7 MR. SMITH: I don't need it. 8 I don't need any speaking. I need 9 to form. And I'm done with it. 10 I've given you plenty of warnings. 11 BY MR. SMITH: 12 Q. Ma'am, do you disagree or 13 agree with what I printed off the website 14 of the University of Vermont Medical 15 Center on ovarian cancer risks? 16 A. I disagree that talcum 17 powder is a dose-related risk in ovarian 18 cancer based upon the peer-reviewed 19 scientific literature. 20 Q. Ma'am, that's -- 21 MR. SMITH: I'm going to 22 object to nonresponsiveness. 23 BY MR. SMITH: 24 Q. Again, do you agree or</p>	<p>1 talc applied to the genitals in its 2 relation to ovarian cancer. You just say 3 it's small. 4 MR. FROST: Objection to 5 form. 6 THE WITNESS: No. I'm 7 saying it's insignificant in the 8 scientific peer-reviewed 9 literature. 10 BY MR. SMITH: 11 Q. Well, what do you define as 12 insignificant? Because any risk to me of 13 getting one of the most deadly forms of 14 cancer, any risk at all that has -- on a 15 product that has no health benefit is 16 significant to me. So we could be 17 defining significant and insignificant in 18 different terms. 19 So are you saying that there 20 is some risk, albeit small, of genital 21 application of talc and ovarian cancer? 22 MR. FROST: Objection to 23 form. 24 THE WITNESS: I am speaking</p>

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<p>1 from a scientist who has looked at</p> <p>2 the risk, relative risks, in</p> <p>3 cohort studies and all of these</p> <p>4 indicate that talcum powder is not</p> <p>5 a significant risk in ovarian</p> <p>6 cancer causation.</p> <p>7 BY MR. SMITH:</p> <p>8 Q. Well, when you say</p> <p>9 significant -- not a significant risk,</p> <p>10 it's still -- your answer implies that</p> <p>11 there is still some risk, okay.</p> <p>12 My question to you is,</p> <p>13 however small or however significant or</p> <p>14 not, is there some risk in its -- in the</p> <p>15 application -- genital application of</p> <p>16 talc and the risk of ovarian cancer?</p> <p>17 MR. FROST: Objection to</p> <p>18 form.</p> <p>19 THE WITNESS: All I'm saying</p> <p>20 is that no, it's not a simple yes</p> <p>21 or no answer, that as a scientist,</p> <p>22 looking at the literature, that</p> <p>23 talc powder is not a statistically</p> <p>24 significant risk factor in the</p>	<p>1 epidemiology primarily.</p> <p>2 BY MR. SMITH:</p> <p>3 Q. Ma'am I'm going to need you</p> <p>4 to be more specific. We're here to get</p> <p>5 your opinions. I don't need</p> <p>6 generalities.</p> <p>7 MR. FROST: I'm going to say</p> <p>8 Okay. She's -- you've got to let</p> <p>9 her finish her answer. She's</p> <p>10 going to follow up.</p> <p>11 THE WITNESS: So let's talk</p> <p>12 about -- I have three reasons for</p> <p>13 that statement, the first and most</p> <p>14 important being the epidemiology;</p> <p>15 that is, the cohort studies, all</p> <p>16 of the four, looking at thousands</p> <p>17 of individuals, do not indicate</p> <p>18 that talcum powder is a risk in</p> <p>19 the development of ovarian cancer,</p> <p>20 and they state it as such.</p> <p>21 I also would base --</p> <p>22 BY MR. SMITH:</p> <p>23 Q. Well -- okay. I'm going</p> <p>24 to -- I want to -- let's just break each</p>
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<p>1 causation of ovarian cancer.</p> <p>2 BY MR. SMITH:</p> <p>3 Q. What do you base that on?</p> <p>4 MR. FROST: Objection to</p> <p>5 form.</p> <p>6 THE WITNESS: All right. Do</p> <p>7 you want me to start with my</p> <p>8 opinions?</p> <p>9 BY MR. SMITH:</p> <p>10 Q. I want to know what you base</p> <p>11 that statement on.</p> <p>12 A. Okay.</p> <p>13 Q. I don't need your opinions.</p> <p>14 I know what they are. We're going to get</p> <p>15 to them. I need to know what do you base</p> <p>16 that the genital application of talc by a</p> <p>17 woman in the epidemiological studies does</p> <p>18 not provide or show a statistically</p> <p>19 significant increased risk of ovarian</p> <p>20 cancer?</p> <p>21 MR. FROST: Objection to</p> <p>22 form.</p> <p>23 THE WITNESS: Again, I can</p> <p>24 emphasize that it's based on</p>	<p>1 one down specifically.</p> <p>2 A. Okay.</p> <p>3 Q. All of those cohort studies</p> <p>4 find a non-statistical increased risk,</p> <p>5 correct?</p> <p>6 MR. FROST: Objection to</p> <p>7 form.</p> <p>8 THE WITNESS: Again, if it's</p> <p>9 not statistical, it can be chance.</p> <p>10 We're talking about a risk less</p> <p>11 than twofold, and in the field of</p> <p>12 epidemiology and in the field of</p> <p>13 biology in general, one looks at a</p> <p>14 risk or a relative risk and it</p> <p>15 generally becomes significant when</p> <p>16 it's above two.</p> <p>17 None of those studies show</p> <p>18 an observed risk or relative risk</p> <p>19 of greater than two.</p> <p>20 BY MR. SMITH:</p> <p>21 Q. So you're saying to have a</p> <p>22 substance be a risk factor for causing</p> <p>23 disease, that you need a relative risk in</p> <p>24 the epidemiology of 2.0 or higher?</p>

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<p>1 A. In general, but you also can 2 exclude risks that are lower than that if 3 they aren't statistically significant. 4 Q. Do you understand that 5 statistical significance in some of those 6 cohort studies might be because they did 7 not have enough people to power the 8 study? 9 MR. FROST: Objection. 10 BY MR. SMITH: 11 Q. Have you looked at any of 12 that? 13 MR. FROST: Objection to 14 form. 15 THE WITNESS: I'm not -- I'm 16 not an epidemiologist. I'm not 17 going to go into the shortcomings 18 of these studies. But there are 19 thousands of individuals and they 20 did have the power to detect other 21 risk factors such as genetic 22 susceptibility. 23 BY MR. SMITH: 24 Q. Well, do you know whether or</p>	<p>1 exposure history, or did the cohort 2 studies just look at frequency or just 3 look at duration? Do you know? 4 MR. FROST: Objection to 5 form. 6 THE WITNESS: I -- again I'd 7 have to go back. If you've got a 8 copy of the studies I'd be happy 9 to comment on that. 10 BY MR. SMITH: 11 Q. Well, let me ask you a 12 question. To get an accurate exposure 13 history, wouldn't you agree with me that 14 you need both frequency and duration to 15 get the most accurate exposure history in 16 a woman? 17 MR. FROST: Objection to 18 form. 19 THE WITNESS: Yeah. That 20 would be a question for an 21 epidemiologist. 22 I can't comment on the 23 relative importance of frequency, 24 duration, or dose.</p>
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<p>1 not these cohorts assessed whether they 2 were genital talc users at one period and 3 followed up to see if they continued as 4 chronic users, or did they just ask them 5 at one point in time? 6 MR. FROST: Objection to 7 form. 8 THE WITNESS: I cannot go 9 through the details. All I can 10 tell you is the bottom lines of 11 these studies. 12 They had fairly reputable 13 talc histories. And they did not 14 show either a statistical increase 15 in relative risk, but they also 16 did not show that there was 17 consistency or dose-response based 18 on frequency or duration. And 19 those are other important 20 variables to consider. 21 BY MR. SMITH: 22 Q. Do you know if any of these 23 studies took into account frequency and 24 duration to get an actual -- accurate</p>	<p>1 BY MR. SMITH: 2 Q. Okay. So if I asked you how 3 many times a year you used genital talc, 4 and you told me how many times a year, 5 you -- you said -- excuse me. 6 How frequently you used 7 talc, and you said twice a week. How 8 would I ever know what the applications 9 were in a year if I don't know the 10 duration? 11 MR. FROST: Objection to 12 form. 13 THE WITNESS: Yeah, that's a 14 question for an epidemiologist. I 15 don't have the actual 16 questionnaires that were provided 17 in these studies. 18 But at the time they were 19 the best questionnaires that could 20 be gleaned in terms of personal 21 history of use. 22 BY MR. SMITH: 23 Q. So you are relying on the 24 cohorts for your opinion on the</p>



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<p>1 epidemiological cohort studies that talc 2 does not significantly increase the risk 3 of ovarian cancer. You cannot tell me in 4 the cohorts how many times they asked the 5 question of -- if these women are genital 6 talc users or followed up to see if they 7 were genital talc users, correct? 8 MR. FROST: Objection to 9 form. 10 THE WITNESS: Again, I'd 11 have to look at the studies. I've 12 read them. I can't recall. There 13 are four of them. And I can't 14 recall whether the questionnaire 15 information was in detail in those 16 publications. 17 The important point is that 18 regardless of the questionnaire, 19 and the talc use that was 20 documented, there was not an 21 increase in dose-response or 22 frequency which gives additional 23 weight to the epidemiology that is 24 the relative risk that talc</p>	<p>1 form. 2 THE WITNESS: Yeah, I -- 3 again, I would have to look at 4 those studies. I don't recall the 5 details. But they attempted to do 6 frequency and dose-response in the 7 studies. 8 BY MR. SMITH: 9 Q. Can you tell me if they 10 allowed for an adequate latency period or 11 follow-up period for the women for a 12 latency -- latent injury and disease like 13 ovarian cancer, do you know if they 14 allowed for an adequate exposure -- 15 latency exposure period? 16 MR. FROST: Objection to 17 form. 18 THE WITNESS: Yeah, 19 certainly the follow-up studies in 20 the Nurses' Health Study did. And 21 since we don't know the latency of 22 development, we -- I can't really 23 answer that question. 24 BY MR. SMITH:</p>
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<p>1 doesn't cause ovarian cancer. 2 BY MR. SMITH: 3 Q. Well, if you're going to use 4 dose-response as one of the factors that 5 you're -- in these cohorts that you're 6 relying on to say that talc does not 7 significantly increase the risk of 8 ovarian cancer, and you can't tell me 9 whether these studies looked at frequency 10 and duration to get an accurate exposure 11 history, that would all factor in to 12 whether you get a dose-response 13 relationship is a little baffling. 14 Do you know whether or not 15 that these four cohort studies that 16 you're relying on, based on lack of 17 dose-response, that talc is not a 18 significant increased risk of ovarian 19 cancer, whether or not all four studies 20 looked at both frequency and duration to 21 get an accurate exposure history that 22 would relate to an adequate dose-response 23 answer to the question? 24 MR. FROST: Objection to</p>	<p>1 Q. So that's -- what else do 2 you rely on to say that talc doesn't 3 significantly increase the risk of 4 ovarian cancer? 5 A. The fact that there have 6 been many animal studies, including those 7 that have injected talc directly into the 8 ovary and those have not given rise to 9 ovarian cancers or mesotheliomas. 10 Q. Did they show adverse 11 cellular changes? 12 A. You'll have to define 13 adverse cellular change. 14 Q. Did they show a reaction to 15 talc? 16 A. I'm sure they must have. 17 Q. Did you look at any other 18 epidemiological studies besides the 19 cohorts to arrive at your opinion that 20 talc does not significantly increase the 21 risk of ovarian cancer? 22 A. Yes. I looked at the 23 case-control studies of which I believe 24 two out of -- I think there are at least</p>

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<p>1 14 or maybe even more, probably between 2 14 and 20 studies, on the majority of 3 those did not show significant risks. 4 And none of them showed an increase with 5 frequency or dose of talc. 6 Q. Did not show a significant 7 increase in risk. 8 A. Mm-hmm. 9 Q. You mean the majority of 10 them did not show a statistical 11 significant increased risk of -- for 12 ovarian cancer? 13 A. The majority of them did not 14 show a statistically significant risk for 15 ovarian cancer that was related to dose 16 and duration of exposure. 17 Q. Well, hold on a second. 18 Let's -- dose-response is totally 19 separate from whether you -- you find a 20 statistically significant increased risk 21 of ovarian cancer from genital talc use 22 in a case-control study. Let's break it 23 down. 24 You're saying the majority</p>	<p>1 A. I haven't looked at them? 2 Q. Any post 2010 animal 3 experience -- experiments. I asked you 4 that in Brower. Had you looked at any -- 5 we talked about IARC in 2010, the 6 monograph. 7 A. Right. 8 Q. And you'd said you had not 9 looked at any animal studies post that 10 monograph; is that correct? 11 A. That had been published 12 since 2010. 13 Q. Yes. 14 A. Correct. 15 Q. And if the monograph is 16 published in 2010, you realize that most 17 of those studies occurred well before 18 2010? 19 A. Yes. 20 Q. Dr. Saenz, is she an 21 epidemiologist? 22 A. I believe that she is an 23 oncologist. 24 Q. Okay. So you relied on the</p>
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<p>1 of the case-control studies did not show 2 a statistically significant increased 3 risk of ovarian cancer from genital talc 4 use? 5 A. Yes. 6 Q. Okay. 7 MR. FROST: Objection to 8 form. 9 BY MR. SMITH: 10 Q. What other epidemiological 11 studies did you look at? Any? 12 A. I looked at the summary of 13 the reports by Dr. Saenz and Dr. Diette 14 which covered these beautifully. So my 15 opinions are certainly bolstered by their 16 reports. 17 Q. So your opinions are 18 bolstered by two defense experts? 19 A. That is after I wrote my 20 report. So my original observations are 21 based on epidemiology and animal 22 experiments and mechanistic studies. 23 Q. You haven't looked at any 24 animal experiments since 2010, right?</p>	<p>1 summary or giving credibility, you said, 2 or I don't know what term you used. 3 Bolstered your opinion by Dr. Saenz who 4 is a gynecological oncologist on the 5 epidemiology. 6 MR. FROST: Objection to 7 form. 8 BY MR. SMITH: 9 Q. Is that correct? 10 A. Yes. I think she gave a 11 very cogent review, and also I believe 12 Dr. Diette, I read his expert report and 13 he gives a, again, I feel a balanced, 14 good overview of the strengths and 15 weaknesses of the studies. 16 Q. Did you do an independent 17 review of the strengths and weaknesses of 18 every epidemiological study that you just 19 discussed, that being the case-control 20 studies and the cohorts? 21 MR. FROST: Objection. 22 THE WITNESS: I did before I 23 wrote my report. I didn't cover 24 it in my report. I looked at</p>

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<p style="text-align: right;">Page 154</p> <p>1 these studies, however. I read</p> <p>2 them, and I looked at their</p> <p>3 abstracts as well for their</p> <p>4 significance.</p> <p>5 BY MR. SMITH:</p> <p>6 Q. What basis do you have to</p> <p>7 rely on the strengths and weaknesses of</p> <p>8 epidemiological study when you say you're</p> <p>9 not an epidemiologist or not an expert in</p> <p>10 epidemiology?</p> <p>11 MR. FROST: Objection to form.</p> <p>12 THE WITNESS: Epidemiology</p> <p>13 is something throughout the years</p> <p>14 that I've had to comment upon in</p> <p>15 all of my published materials in</p> <p>16 trying to make correlations</p> <p>17 between what I observe and what's</p> <p>18 been observed in epidemiology.</p> <p>19 So I am not one to question</p> <p>20 or critique the studies in terms</p> <p>21 of their individual positive or</p> <p>22 negative features. But all the</p> <p>23 studies say the same thing,</p> <p>24 especially the cohort studies.</p>	<p style="text-align: right;">Page 156</p> <p>1 specific strengths and weaknesses of the</p> <p>2 Nurses' Health studies that you examined</p> <p>3 to give weight or non-weight to those</p> <p>4 particular cohort studies.</p> <p>5 A. Okay.</p> <p>6 MR. FROST: Objection to</p> <p>7 form.</p> <p>8 THE WITNESS: So I'm going</p> <p>9 to give two without going back to</p> <p>10 the papers, which aren't in front</p> <p>11 of me.</p> <p>12 There would not be the</p> <p>13 issues of recall bias in those</p> <p>14 studies as there would have been</p> <p>15 in case-control studies.</p> <p>16 And there would not have</p> <p>17 been misclassification of tumors</p> <p>18 because these are prospective</p> <p>19 studies.</p> <p>20 Other than that, I could not</p> <p>21 comment unless I have the study in</p> <p>22 front of me.</p> <p>23 BY MR. SMITH:</p> <p>24 Q. That -- your statement that</p>
<p style="text-align: right;">Page 155</p> <p>1 BY MR. SMITH:</p> <p>2 Q. Well, if you're going to</p> <p>3 give weight to certain evidence and not</p> <p>4 weight to certain evidence to arrive at</p> <p>5 an opinion, and you're not -- you're not</p> <p>6 specifically look -- and are able to look</p> <p>7 at the strengths and weaknesses of these</p> <p>8 epidemiological studies, how do you</p> <p>9 arrive at an opinion about the</p> <p>10 epidemiological studies in general?</p> <p>11 MR. FROST: Objection to</p> <p>12 form.</p> <p>13 THE WITNESS: As I</p> <p>14 emphasize, I look at the relative</p> <p>15 risk. I look at whether there's a</p> <p>16 dose-response relationship in</p> <p>17 terms of talc use. And there are</p> <p>18 no other conclusions from these</p> <p>19 studies that I can make other than</p> <p>20 talcum powder does not pose a risk</p> <p>21 that's significant in the</p> <p>22 development of ovarian cancers.</p> <p>23 BY MR. SMITH:</p> <p>24 Q. I would like to know the</p>	<p style="text-align: right;">Page 157</p> <p>1 you just made is a statement that could</p> <p>2 be made generally about any cohort versus</p> <p>3 case-control study, correct?</p> <p>4 MR. FROST: Objection.</p> <p>5 THE WITNESS: You'd have to</p> <p>6 ask an epidemiologist about that.</p> <p>7 BY MR. SMITH:</p> <p>8 Q. I want to know the specific</p> <p>9 shortcomings of the Nurses' Health</p> <p>10 studies and the other two cohort studies</p> <p>11 that you considered before giving any</p> <p>12 weight to those studies for your opinion</p> <p>13 that talc does not significantly increase</p> <p>14 the risk of ovarian cancer?</p> <p>15 MR. FROST: Objection.</p> <p>16 THE WITNESS: Again, I did</p> <p>17 not see specific weaknesses in</p> <p>18 those studies.</p> <p>19 BY MR. SMITH:</p> <p>20 Q. Okay. Can talc be safely</p> <p>21 absorbed in a woman's vagina?</p> <p>22 A. I don't think there's any</p> <p>23 evidence for talc absorption in a vagina.</p> <p>24 MR. FROST: What number are</p>

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<p>1 we on?</p> <p>2 MR. SMITH: 18.</p> <p>3 (Document marked for</p> <p>4 identification as Exhibit</p> <p>5 Mossman-18.)</p> <p>6 BY MR. SMITH:</p> <p>7 Q. Have you ever seen any</p> <p>8 internal documents of the defendants, of</p> <p>9 Johnson &amp; Johnson, Imerys, Luzenac?</p> <p>10 A. I have not.</p> <p>11 Q. Have you asked to see any of</p> <p>12 them?</p> <p>13 A. No.</p> <p>14 Q. Would you like to have seen</p> <p>15 any of them?</p> <p>16 A. I wouldn't know what to ask</p> <p>17 for.</p> <p>18 Q. Well, if they're scientific</p> <p>19 and otherwise -- documents from the</p> <p>20 company that you're defending from</p> <p>21 scientists from the company, would you</p> <p>22 have liked to have seen those?</p> <p>23 MR. FROST: Objection to</p> <p>24 form.</p>	<p>1 bottom right there's a Bates number. It</p> <p>2 says J&amp;J, and it's got some numbers. And</p> <p>3 that's just to indicate that they</p> <p>4 produced this to me.</p> <p>5 And what this document is,</p> <p>6 Doctor, it's about a cornstarch</p> <p>7 substitute that they were looking at in</p> <p>8 testing. And I want to go to the last</p> <p>9 page. It's called it's called a Dry Flo</p> <p>10 product. And in the second paragraph,</p> <p>11 "Since the meeting, Ashton</p> <p>12 established" -- and he is an employee of</p> <p>13 Johnson &amp; Johnson -- "the largest</p> <p>14 commercial use of Dry-Flo are in vitamin</p> <p>15 A manufacturer (5 percent in finished</p> <p>16 product) and as a condom lubricant where</p> <p>17 it had replaced talc because it was found</p> <p>18 to be safely absorbed in the vagina,</p> <p>19 whereas of course talc was not."</p> <p>20 Do you have an opinion</p> <p>21 whether talc can be safely absorbed in a</p> <p>22 woman's vagina?</p> <p>23 MR. FROST: Objection to</p> <p>24 form.</p>
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<p>1 THE WITNESS: Yeah, I can't</p> <p>2 think of specific instances.</p> <p>3 Again, I'm not looking at internal</p> <p>4 documents to render my opinions.</p> <p>5 I'm looking at the peer-reviewed</p> <p>6 literature.</p> <p>7 BY MR. SMITH:</p> <p>8 Q. This is an article --</p> <p>9 actually, it's an internal memo from</p> <p>10 Johnson &amp; Johnson. You see the title</p> <p>11 is -- subject is "Cornstarch</p> <p>12 development." Would you agree with me</p> <p>13 that cornstarch powder, there's no</p> <p>14 reported ill effects of cornstarch powder</p> <p>15 and ovarian cancer risk?</p> <p>16 A. I have not seen that in the</p> <p>17 literature. But I have not done a review</p> <p>18 of cornstarch through PubMed.</p> <p>19 Q. You see, "Cornstarch</p> <p>20 development, February 21st, 1964," at the</p> <p>21 top.</p> <p>22 Do you see that?</p> <p>23 A. I do.</p> <p>24 Q. And if you look at the</p>	<p>1 BY MR. SMITH:</p> <p>2 Q. I think you stated earlier.</p> <p>3 I thought you said that you couldn't see</p> <p>4 any reason why it couldn't be.</p> <p>5 MR. SMITH: Could we go back</p> <p>6 to that question?</p> <p>7 THE WITNESS: I don't know</p> <p>8 what they mean by absorbed safely</p> <p>9 in the vagina. Talc enters and</p> <p>10 other things enter cells. They're</p> <p>11 not absorbed. So I have -- I'm</p> <p>12 not sure what the scientific</p> <p>13 information is here.</p> <p>14 BY MR. SMITH:</p> <p>15 Q. If you believe that talc</p> <p>16 could be safely absorbed in a woman's</p> <p>17 vagina, you would be in disagreement with</p> <p>18 Mr. Ashton that wrote this letter on</p> <p>19 February 21, 1964, as an employee of</p> <p>20 Johnson &amp; Johnson, correct?</p> <p>21 MR. FROST: Objection to</p> <p>22 form.</p> <p>23 THE WITNESS: Yeah, I have</p> <p>24 not -- I can't comment on this,</p>

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<p>1 because I'm unaware of any studies 2 with either cornstarch or talc 3 absorption in the vagina. I don't 4 know what that means. 5 BY MR. SMITH: 6 Q. Can talc cause inflammation? 7 MR. FROST: Objection to 8 form. 9 THE WITNESS: Again, it 10 depends upon the circumstances and 11 the dose and the site of 12 application. 13 BY MR. SMITH: 14 Q. Can talc cause inflammation? 15 MR. FROST: Objection to 16 form. 17 THE WITNESS: Yeah. You'd 18 have to ask me in terms of the 19 dose or give me an example. 20 BY MR. SMITH: 21 Q. Is talc capable of causing 22 inflammation in human tissue? 23 MR. FROST: Objection to 24 form.</p>	<p>1 broadest sense. It would depend 2 upon the dose, duration from the 3 oxidant stress. 4 BY MR. SMITH: 5 Q. Do you have an opinion on 6 whether inhaled particles can reach the 7 ovaries? 8 A. That has not been shown. 9 So no one has really looked 10 at that in detail. But the answer is 11 that most of the information suggests 12 that an inhaled particle is dealt with 13 locally, rather than disseminated. 14 Although there's evidence in the 15 bloodstream that there is dissemination 16 of materials throughout the body. 17 Q. Have you ever conducted a 18 study on cosmetic talc and ovarian 19 cancer? 20 A. I haven't used cosmetic 21 talc, as I've said previously. 22 Q. Have you ever published on 23 asbestos and ovarian cancer? 24 A. No. But I've published</p>
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<p>1 THE WITNESS: In human 2 tissue? It's been used in 3 pleurodesis if that's what you're 4 talking about, which induces an 5 acute inflammation that's 6 beneficial to patients with 7 malignant effusions. 8 BY MR. SMITH: 9 Q. Can chronic inflammation 10 lead to ovarian cancer? 11 MR. FROST: Objection to 12 form. 13 THE WITNESS: There is no 14 evidence that it's linked to 15 causation. 16 So I can't comment on that. 17 It hasn't been shown. 18 BY MR. SMITH: 19 Q. Can oxidative stress lead to 20 ovarian cancer? 21 MR. FROST: Objection to 22 form. 23 THE WITNESS: Yeah, I 24 couldn't agree with that in the</p>	<p>1 studies on asbestos, on ovarian 2 epithelial cells. 3 Q. Have you ever published on 4 asbestos and ovarian cancer? 5 MR. FROST: Objection to 6 form. 7 THE WITNESS: Yeah, I did 8 state, and I believe it's in the 9 Shukla and Hillegass paper, 10 references on ovarian cancer and 11 asbestos. 12 BY MR. SMITH: 13 Q. Can you turn to the Brower 14 deposition Page 134? 15 A. Mm-hmm. 16 Q. Line 10. 17 "Question: Have you ever 18 conducted a study on asbestos and ovarian 19 cancer? 20 "Answer: No." 21 Has that changed since 22 October of 2000 -- 23 A. I'm sorry, could you point 24 that out again?</p>

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<p>1 Q. Sure. Line 10, on Page 134. 2 "Question: Have you ever 3 conducted a study on asbestos and ovarian 4 cancer?" 5 And what was your answer? 6 A. No. I haven't looked at 7 ovarian cancer, per se. 8 Q. Can I rely on that testimony 9 in Brower as being accurate? 10 A. Pardon me? 11 Q. Can I rely on the testimony 12 in this Brower case that I just read as 13 being accurate? 14 A. Yes. I've not looked at -- 15 at asbestos and ovarian cancer. I 16 emphasize that I've looked at asbestos 17 effects on ovarian epithelial case. 18 Q. Have you ever given a speech 19 or seminar on talc and ovarian cancer? 20 A. No. 21 Q. Have you ever done -- 22 conducted a study on fibrous talc and its 23 carcinogenicity related to ovarian 24 cancer?</p>	<p>1 Q. Have you ever conducted a 2 study on EMPs and ovarian cancer? 3 A. Again, I haven't used 4 ovarian cancer cells, just ovarian 5 epithelial cells that develop into 6 cancer. 7 Q. And EMPs can cause 8 epigenetic changes in human cells that 9 may lead to cancer, correct? 10 MR. FROST: Objection to 11 form. 12 THE WITNESS: Again, it 13 depends on the EMP. That's true 14 for amphibole asbestos fibers. 15 BY MR. SMITH: 16 Q. Well, it's true for any 17 elongated mineral particle, correct? 18 A. What -- 19 Q. Not just asbestos? 20 A. That does what? 21 Q. That cause can give rise to 22 epigenetic changes in human cells that 23 may lead to cancer. 24 A. No. There are other --</p>
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<p>1 A. You're going to have to be 2 specific. When you talk about ovarian 3 cancer studies, are you talking about 4 studies on ovarian epithelial cells or 5 are you talking about studies on cancer 6 cells? 7 Q. Can you look at Page 136 of 8 your Brower testimony? 9 A. Sure. 10 Q. Line 4. "And you've never 11 conducted a study on fibrous talc and its 12 carcinogenicity to ovarian cancer, 13 correct?" 14 "Answer: I have not used 15 ovarian cells in studies with fibrous 16 talcs." 17 Is that still true today? 18 A. Yes. Fibrous talcs have not 19 been evaluated in ovarian epithelial 20 cells. 21 Q. Have you ever conducted a 22 study on asbestiform talc and ovarian 23 cancer? 24 A. No.</p>	<p>1 there are materials that we and others 2 have used as negative controls in our 3 studies that are fibrous and are EMPs 4 that don't give rise to precancerous 5 changes. 6 Q. Have you ever conducted a 7 study on heavy metals and ovarian cancer? 8 A. I haven't. 9 Q. Can you give an opinion on 10 whether heavy metals contribute to cause 11 ovarian cancer? 12 A. Yes. I have not seen any 13 studies where heavy metals have given 14 rise to ovarian cancers in animals. 15 Q. You're saying there are no 16 studies on heavy metals and ovarian 17 cancer risk? 18 A. I -- 19 MR. FROST: Objection to 20 form. 21 THE WITNESS: The -- I have 22 not seen any studies that have 23 given rise to ovarian cancers. 24 There are many studies with</p>

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<p>1 animals using heavy metals at a 2 variety of high concentrations and 3 methods of injection or 4 inhalation. And these have not 5 given rise to ovarian cancers. 6 BY MR. SMITH: 7 Q. What about, do you have an 8 opinion whether fibrous talc can cause 9 ovarian cancer? 10 MR. FROST: Objection to 11 form. 12 THE WITNESS: Based upon my 13 research with lung epithelial 14 cells, I would argue against that 15 being a true statement. 16 BY MR. SMITH: 17 Q. So you are extrapolating 18 your studies on lung cells to whether 19 fibrous talc can cause ovarian cancer? 20 A. I'm not extrapolating. I'm 21 saying that fibrous talcs as evaluated in 22 my studies and in animal studies have not 23 given rise to ovarian cancers. 24 Q. You would --</p>	<p>1 If they were relevant to 2 ovarian epithelial cells, I would have 3 seen responses to these materials in my 4 studies. 5 Q. But you've never tested 6 ovarian cells for that? 7 A. No. But as I emphasize, 8 I've got -- I've gotten the same 9 responses in lung epithelial and 10 mesothelial cells. So there's different 11 cell types that are important. 12 Again, epithelial cells are 13 the cells that give rise to cancers. So 14 ovarian epithelial cells are probably 15 very similar in their responses to lung 16 epithelial cells. 17 Q. Probably? What are you 18 basing that on? Probably? 19 MR. FROST: Objection. 20 THE WITNESS: Yeah, I'm 21 basing it on historical studies 22 with asbestos fibers that have 23 shown the same pre-neoplastic 24 effects in our laboratory, in</p>
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<p>1 A. So that would argue against 2 the connection. 3 Q. Do you know whether fibrous 4 talc or other minerals act differently in 5 pleural cells versus ovarian cells or 6 peritoneal cells? 7 MR. FROST: Objection to 8 form. 9 THE WITNESS: No, they turn 10 on the same signaling pathways in 11 lung epithelial cells and 12 mesothelial cells. 13 BY MR. SMITH: 14 Q. Do you know whether or not 15 fiber dimensions, crystalline structures, 16 shape tensile strength of asbestos, have 17 any relevance to ovarian cancer? 18 A. Could we go through these 19 one at a time? 20 Q. Sure. 21 A. So, I would argue that these 22 different properties are properties of 23 asbestos fibers that have given rise to 24 mesotheliomas or lung cancers.</p>	<p>1 other laboratories that have 2 looked at a host or a huge range 3 of different cell types. And the 4 basic phenomena, the properties of 5 those asbestos fibers are the same 6 in terms of their biological 7 reactivity in a host of different 8 cell types. 9 BY MR. SMITH: 10 Q. But you've never done that 11 with ovarian cancer cells, right? 12 A. I have -- 13 Q. Ovarian cells, excuse me. 14 A. Yeah. 15 Q. You have not done that with 16 ovarian cells? 17 A. I have only looked at 18 fibrous -- I should say non-fibrous talc 19 in ovarian epithelial cells. 20 Q. And when we were talking 21 about fibrous talc earlier, you've never 22 done any studies on fibrous talc correct? 23 A. I had done studies on 24 fibrous talcs.</p>

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<p style="text-align: right;">Page 174</p> <p>1 Q. The one study in New York, 2 correct? 3 A. The study with Dr. Wiley 4 where we looked in two different cell 5 types at three different preparations of 6 fibrous talcs. 7 Q. Is crystalline silica a 8 fibrogenic dust that causes oxidative 9 damage to cells? 10 A. It does at very high 11 concentrations. 12 Q. Have you ever performed 13 rodent studies on talc? 14 A. I have not. 15 Q. You've never performed any 16 rodent inhalation studies on talc and its 17 relation to ovarian cancer; is that true? 18 A. I have not performed the 19 studies. 20 Q. Same for cleavage fragments? 21 A. I have not used cleavage 22 fragments in rodent inhalation studies. 23 Q. You've not performed studies 24 on whether or not asbestos cleavage</p>	<p style="text-align: right;">Page 176</p> <p>1 What do you base that on? 2 A. The fact that Zazenski and 3 others describe it as cosmetic and 4 pharmaceutical talcs are 98 percent pure 5 as opposed to industrial talcs from the 6 mining sites. 7 Q. You're relying on Zazenski, 8 who was an employee of Imerys, who is 9 involved in talc litigation, who 10 published in the Regulatory Toxicology 11 and Pharmacology publication that we 12 discussed earlier? 13 MR. FROST: Objection to 14 form. 15 THE WITNESS: That's only 16 one paper. I believe that this is 17 summarized in IARC 2010. It says 18 the exact same thing. 19 BY MR. SMITH: 20 Q. Well, hold on. You said you 21 hadn't seen any internal documents. 22 Where are you seeing the Zazenski stuff? 23 A. Zazenski is a paper that I 24 pulled from the literature in a</p>
<p style="text-align: right;">Page 175</p> <p>1 fragments cause ovarian cancer, correct? 2 A. I have not looked at 3 cleavage fragments in ovarian epithelial 4 cells, that's correct. 5 Q. And you do not know whether 6 the biodurability of asbestos or talc 7 have any relevance to the development of 8 ovarian cancer, correct? 9 A. That hasn't been examined 10 since we don't know the latency period of 11 ovarian cancers to begin with. 12 Q. Do you know what Baby Powder 13 is made of? 14 MR. FROST: Objection to 15 form. 16 THE WITNESS: Yeah. I -- I 17 believe it's indicated as such on 18 the label. 19 In general, yes. I'm aware 20 that it has some fragrance 21 chemicals, but it's also a very 22 pure type of talc. 23 BY MR. SMITH: 24 Q. A very pure type of talc.</p>	<p style="text-align: right;">Page 177</p> <p>1 peer-reviewed journal. 2 Q. The Regulatory Toxicology 3 and Pharmacology -- 4 A. Talked about -- yes. 5 Q. -- publication? 6 A. Yes. That's one source. 7 IARC also summarizes the 8 properties of talcs in its monograph in 9 several places in the 2010 document. And 10 has additional references. 11 Q. What is Shower to Shower 12 made of? 13 A. I would have to look at the 14 label. 15 Q. Do you know? 16 A. I don't. 17 Q. Do you know what percentage 18 of Baby Powder is talc and what is 19 other -- other constituents? 20 A. I don't know the percentage 21 values. 22 Q. None of your studies 23 concerned Baby Powder or Shower to 24 Shower, correct?</p>

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<p>1 A. I have not used those 2 specifically. 3 Q. None of your studies include 4 cosmetic-grade talc or talc from any mine 5 that has been sourced from these two 6 products, correct? 7 MR. FROST: Objection to 8 form. 9 THE WITNESS: Again, I 10 worked with industrial talcs, one 11 a Barrett mining talc. I don't 12 know whether it's been sourced for 13 cosmetic talcs. 14 BY MR. SMITH: 15 Q. Well, you've never worked 16 with talc from Vermont, correct, 17 cosmetic-grade talc from Vermont? 18 A. That's correct. 19 Q. You've never worked with 20 cosmetic-grade talc from China, correct? 21 A. That's correct. 22 Q. You've never worked with 23 cosmetic-grade talc from Italy, correct? 24 A. Correct.</p>	<p>1 form. 2 THE WITNESS: None, to my 3 knowledge. 4 BY MR. SMITH: 5 Q. You've never seen the report 6 of Dr. Longo? 7 A. I'm aware he has one. I 8 have not reviewed it for this case. 9 Q. You didn't think it was 10 important to know what the testing 11 results were from the '60s, '70s, '80s, 12 '90s, and 2000s from Johnson &amp; Johnson 13 bottles from their own possession from 14 their own museum regarding the presence 15 of asbestos or not? 16 MR. FROST: Objection to 17 form. 18 THE WITNESS: Yeah, I had no 19 information suggesting that 20 asbestos was found in cosmetic 21 talcs. And I would assume that 22 Dr. Longo's information is 23 court-related and not in the 24 peer-reviewed scientific</p>
Page 179	Page 181
<p>1 Q. Okay. You've never 2 performed any animal inhalation studies 3 with Baby Powder or Shower to Shower, 4 correct? 5 A. That's correct. 6 Q. And you've never performed 7 any animal inhalation studies with 8 cosmetic-grade talc or talc from any mine 9 that has been sourced from these two 10 products, correct? 11 A. That's correct. 12 Q. You've never performed any 13 work or studies on Johnson &amp; Johnson's 14 Baby Powder or Shower to Shower, correct? 15 A. Correct. 16 Q. Do you know what the fiber 17 or mineral size of these two products 18 are? 19 A. I have not looked at fiber 20 size dimensions of cosmetic talcs, no. 21 Q. What types of asbestos have 22 been found in Johnson &amp; Johnson Baby 23 Powder and Shower to Shower? 24 MR. FROST: Objection to</p>	<p>1 literature. So for that reason, I 2 wouldn't have looked at it. 3 BY MR. SMITH: 4 Q. Well, the fact that you have 5 an opinion that cosmetic-grade talc, 6 which you've never done any studies on, 7 is not a risk factor or cause of ovarian 8 cancer, and those are your opinions in 9 this case as you stated earlier, don't 10 you think it would be pretty important to 11 know if there are any carcinogenic 12 substances that are found in the products 13 that are at issue in this case before 14 rendering that opinion? 15 MR. FROST: Objection to 16 form. 17 THE WITNESS: Again, that's 18 why I read the IARC information, 19 and IARC in 2010 says that there 20 are no asbestos fibers in cosmetic 21 talcs. 22 BY MR. SMITH: 23 Q. Have you reviewed the 24 internal documents of Johnson &amp; Johnson</p>

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<p>1 and Imerys to see the numerous times that 2 different types of asbestos have been 3 found in their products, in their own 4 internal testing? 5 MR. FROST: Objection to 6 form. 7 THE WITNESS: No. I 8 wouldn't know what documents to 9 even ask for. 10 BY MR. SMITH: 11 Q. Don't you think it's 12 important -- again, if you're going to 13 render an opinion about -- and we're 14 talking about -- at issue in this case is 15 cosmetic-grade talc, not industrial, 16 right? 17 A. Correct. 18 Q. And we're talking about two 19 products, Baby Powder and Shower to 20 Shower, applied to a woman's genital area 21 and that causing ovarian cancer, correct? 22 A. Again, I emphasize that it 23 wouldn't make any difference whether 24 there was a small amount of asbestos in</p>	<p>1 A. That there is not a 2 significantly increased risk of ovarian 3 cancer that's related to dose dependency 4 of talc use in these studies. 5 Q. Let's -- let's get it 6 straight. 7 So the meta-analyses that 8 you looked at in forming the basis of 9 your opinion that talc does not cause or 10 is a risk factor for ovarian cancer, you 11 based in part on also the meta-analyses 12 for which you say those meta-analyses 13 state consistently the same thing, that 14 talc -- in those studies show that talc 15 does not cause -- those studies did not 16 show that talc increases the risk of 17 ovarian cancer and that -- that finding 18 is statistically significant, correct? 19 MR. FROST: Objection to 20 form. 21 THE WITNESS: We'd have to 22 go back to the papers. I'm aware 23 that the meta-analyses that I've 24 looked at may have been for the</p>
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<p>1 there, in terms of my opinion. Those 2 talcs were used by individuals, I'm sure, 3 in the Women's Health Initiative, the 4 Gonzalez study and the Nurses' Health 5 study used cosmetic talcs, and they 6 didn't report an increase in ovarian 7 cancers. 8 So in attempting to go back 9 in time and point out discovery of a few 10 fibers is not conclusive evidence in any 11 regard in terms of my opinions. 12 Q. You did not look at any 13 meta-analyses in this case, did you? 14 A. Meta-analyses? I certainly 15 did. I looked at meta-analyses in terms 16 of the epidemiology. 17 Q. What did the meta-analyses 18 of talc and ovarian cancer risk reveal? 19 A. The meta-analyses with the 20 exception of, I believe it's 21 Penninkilampi who eliminated one of the 22 more recent cohort studies, all say the 23 same thing. 24 Q. What's that?</p>	<p>1 case-related studies or the 2 case-control studies. And with 3 the exception of Penninkilampi, 4 the meta-analyses that I looked at 5 did not suggest an increase in 6 ovarian cancer that was associated 7 with talc use. 8 BY MR. SMITH: 9 Q. Okay. You do not know if 10 there are EMPs in Baby Powder or Shower 11 to Shower, do you? 12 A. I don't. 13 Q. You don't know if there are 14 EMPs in cosmetic-grade talc, do you? 15 A. I don't. 16 Q. Do you know if scientists 17 have found EMPs in Baby Powder or Shower 18 to Shower? 19 MR. FROST: Objection to 20 form. 21 THE WITNESS: Yeah, I 22 haven't seen it in the 23 peer-reviewed scientific 24 literature.</p>

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<p>1 BY MR. SMITH: 2 Q. You can't tell me whether or 3 not there's asbestiform talc in Baby 4 Powder or Shower to Shower, correct? 5 MR. FROST: Objection to 6 form. 7 THE WITNESS: Again, it 8 hasn't been indicated as such 9 and -- or published in the 10 peer-reviewed scientific 11 literature. 12 BY MR. SMITH: 13 Q. And again, you have not 14 looked at the reports of Dr. Longo or 15 Rigler. 16 Have you seen the -- the 17 publication of Dr. Blount? 18 A. I have -- the -- is this a 19 publication of many years ago, 40 years 20 ago? 21 Q. It's in the 1990s. 22 A. I did look at that at one 23 point, yes. 24 Q. Okay. What did it -- what</p>	<p>1 Q. Would you have liked to have 2 known that or seen that when you were 3 reviewing the study? 4 MR. FROST: Objection to 5 form. 6 THE WITNESS: Well, my -- 7 probably not. Because I know that 8 talc and fiber identification and 9 the methods used have become 10 increasingly more significant in 11 terms of newer approaches. So I 12 wouldn't have been interested in 13 her work, which I believe was 40 14 or 50 years ago and had 15 questionable use of the 16 appropriate techniques. 17 BY MR. SMITH: 18 Q. Okay. You are aware that -- 19 you are not an expert in testing for 20 asbestos, are you, the presence of 21 asbestos? 22 A. I'm not. 23 Q. Did you understand that the 24 Blount method is a recognized method for</p>
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<p>1 did it say? 2 A. It was confusing in terms of 3 her use of the nomenclature of talc, 4 which she referred to as sometimes 5 acicular, other types fibrous. It was 6 difficult to interpret that paper. 7 Q. So, you don't know whether 8 or not they talked about whether there 9 was asbestiform in -- found in Johnson &amp; 10 Johnson's Baby Powder or Shower to Shower 11 products? 12 MR. FROST: Objection to 13 form. 14 THE WITNESS: Yeah, I don't 15 recall that this paper identified 16 the products that she examined. 17 BY MR. SMITH: 18 Q. Okay. Have you ever seen 19 any other testimony or asked for any 20 other testimony or been shown any 21 testimony that reveals what the source of 22 her study was, that being talc? 23 A. I -- yeah, I don't recall. 24 Recently, no.</p>	<p>1 testing for asbestos in -- in certain 2 products? 3 MR. FROST: Objection to 4 form. 5 THE WITNESS: Again, I 6 emphasize that she used a 7 concentration method to 8 concentrate materials and I 9 believe that is accepted, but has 10 been questioned by scientists. 11 I am quite certain that she 12 didn't use other approaches such 13 as zonal access x-ray diffraction, 14 which is state of the art today, 15 for fiber identification. 16 BY MR. SMITH: 17 Q. Do you know if Dr. Longo and 18 Dr. Rigler did that on the products that 19 were provided them by Johnson &amp; Johnson? 20 MR. FROST: Objection to 21 form. 22 THE WITNESS: I don't know. 23 BY MR. SMITH: 24 Q. And again, you are not an</p>

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<p>1 expert in identifying asbestos in 2 materials, right? 3 A. I don't look at air samples 4 or lung digests for asbestos fibers. 5 Q. Or -- or evaluate, for 6 instance, Baby Powder or Shower to Shower 7 to determine whether asbestos, heavy 8 metal, silica, were present, correct? 9 A. I don't do that. I'm a 10 biologist. 11 Q. Do you know whether or not 12 there are carcinogenic heavy metals in 13 Baby Powder and Shower to Shower? 14 A. Again, the carcinogens that 15 had been listed by Dr. Selikoff in her 16 report have not given rise in 17 epidemiology or animal studies to ovarian 18 cancers. 19 Q. Do you know whether or not 20 there is carcinogenic crystalline silica 21 in Baby Powder or Shower to Shower? 22 A. I don't. 23 Q. We talked about the 24 different types of asbestos earlier. Do</p>	<p>1 document before, Doctor? 2 A. I have. 3 Q. And this is on asbestos, 4 chrysotile, amosite, crocidolite, 5 tremolite, actinolite, and anthophyllite, 6 and this is the IARC monograph, right? 7 A. Yes. 8 Q. And if you flip to Page 253, 9 it's Page 35 of 92 down at the bottom. 10 If you look at the very bottom of the 11 page, Doctor. It discusses cancer of the 12 ovary. 13 A. 35 of 92? 14 Q. Yes, ma'am. 15 A. Okay. 16 Q. Do you see that? 17 A. Yes. 18 Q. And then it goes on, on 19 Page 76 of 92, for the evaluation. It's 20 near the end. It states, "There is 21 sufficient evidence in humans for the 22 carcinogenicity of all forms of asbestos, 23 chrysotile, crocidolite, amosite, 24 tremolite, actinolite, and</p>
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<p>1 you recall that? 2 A. I do. 3 Q. And we were -- I was asking 4 you whether or not you thought that all 5 types of asbestos were carcinogenic to 6 humans. Do you recall that? 7 A. I do. 8 Q. And we discussed the NTP and 9 IARC have determined that all forms of 10 asbestos are known human carcinogens, 11 correct? 12 MR. FROST: Objection to 13 form. 14 THE WITNESS: That is stated 15 in terms of their regulatory 16 policies, yes. 17 BY MR. SMITH: 18 Q. I will attach, the next 19 numbered exhibit is 19. 20 (Document marked for 21 identification as Exhibit 22 Mossman-19.) 23 BY MR. SMITH: 24 Q. And you've seen this</p>	<p>1 anthophyllite." 2 A. Could you point -- 3 MR. FROST: I was going to 4 say, where are you reading from? 5 THE WITNESS: Yeah. 6 MR. SMITH: I'm sorry. I 7 might not have said it. I might 8 have been thinking it and didn't 9 say it. 10 BY MR. SMITH: 11 Q. Page 76 of 92, down at the 12 bottom -- 13 MR. FROST: Oh, under 14 evaluation? 15 MR. SMITH: Yeah, under 16 evaluation. 17 THE WITNESS: 76. 18 MR. SMITH: It's under 19 evaluation. 20 THE WITNESS: Okay. 21 MR. FROST: Now we are on 22 the same page. 23 BY MR. SMITH: 24 Q. All right. And it says,</p>

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<p>1 "There is sufficient evidence of" -- "in 2 humans for the carcinogenicity of all 3 forms of asbestos. Asbestos causes 4 mesothelioma and cancer of the lung, 5 larynx, and ovary." 6 Do you see that? 7 A. Yes. 8 Q. And that's what we were 9 talking about earlier when I was talking 10 about IARC? 11 A. Yes. 12 Q. And then it says at the 13 bottom, "All forms of asbestos, 14 chrysotile, crocidolite, amosite, 15 tremolite, actinolite, and anthophyllite, 16 are carcinogenic to humans Group 1." 17 Do you see that? 18 A. I do. 19 Q. Is that what we were 20 discussing earlier? 21 A. Yes. 22 Q. We talked about earlier that 23 talc with asbestiform fibers is also a 24 known human carcinogen as well by IARC;</p>	<p>1 bulletin, right, of Bulletin 62 of NIOSH? 2 A. I did. 3 Q. And you weren't aware that 4 Dr. -- that Dr. Michaels served on that 5 as well, with you? You weren't aware of 6 that, right? 7 A. He wasn't on the committee 8 meetings that I attended. So I'm not 9 sure what -- where he was. He may have 10 been someone that -- okay, he may have 11 been someone that served in some 12 capacity. I just don't recall it. 13 (Document marked for 14 identification as Exhibit 15 Mossman-20.) 16 BY MR. SMITH: 17 Q. I'm going to attach as 18 Exhibit 20. This is current intelligence 19 Bulletin 62, "Asbestos fibers and other 20 elongated mineral particles, state of the 21 science and roadmap for research." 22 And this was put out by the 23 Department of Health and Human Services 24 and NIOSH, correct?</p>
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<p>1 is that correct? 2 A. They classify it as such. 3 Q. And we went through also the 4 Prop 65 listing. Do you recall that for 5 asbestiform talc? 6 A. Yes. I'm not sure what that 7 said exactly, but I don't think we 8 discussed that. 9 Q. Well, let's discuss it. It 10 says, "Talc containing asbestiform 11 fibers." It's Exhibit 15. 12 It says, "Chemical listing 13 details." And it says, "Listed as 14 causing," and it says "cancer." 15 Do you see that? And date 16 of listing was on 4/1/1990? 17 A. Yes. 18 Q. Okay. And do you remember 19 us talking earlier, I asked you about if 20 you knew David Michaels, if he was -- and 21 we went through his book, his chapter in 22 the book on Regulatory Toxicology and 23 Pharmacology. And I asked you, you 24 served as a peer reviewer of this</p>	<p>1 A. Yes. 2 Q. And NIOSH is the scientific 3 arm of OSHA; is that correct? 4 A. Yes, it is. 5 Q. Responsible for health and 6 safety of American workers; is that 7 correct? 8 A. That's OSHA. NIOSH is more 9 a research body. 10 Q. And if you look at XVII. 11 It's in the front page. I guess that 12 would be 17. 13 A. Okay. 14 Q. It says -- do you see 15 "acknowledgments" at the top? Down at 16 the bottom right corner, Doctor? 17 A. Yes. 18 Q. XVII. It says peer 19 reviewers. Do you see that? 20 It says, "NIOSH greatly 21 appreciates the time and efforts of 22 expert peer reviewers who provided 23 comments and suggestions on the initial 24 publicly disseminated draft of the</p>

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<p>1 roadmap February 7, 2007, version." 2 Do you see that? 3 A. Yes, I do. 4 Q. And do you see David 5 Michaels, Ph.D. MPH, George Washington 6 University listed on that page? 7 A. I do. 8 Q. And then on the next page 9 you are listed on the top, correct? 10 A. Mm-hmm. 11 Q. Okay. If we go to -- let's 12 see. If you look at Page 33, Doctor. If 13 you look at the bottom right in the 14 footnote, if you go two, four, six -- six 15 lines down. It says, "The National 16 Toxicology Program, NTP, 2005, of which 17 NIOSH is a member, has determined that 18 asbestos in all commercial forms of 19 asbestos are known to be human 20 carcinogens based on sufficient evidence 21 of carcinogenicity in humans." 22 Do you see that? 23 MR. FROST: Want me to help 24 you?</p>	<p>1 internally by Johnson &amp; Johnson, Imerys 2 internally, or by Dr. Longo? 3 A. I don't. 4 Q. If I told you they were 5 tremolite, anthophyllite, and actinolite, 6 the majority of what was found, the vast 7 majority, you wouldn't have any basis or 8 any knowledge regarding that, right? 9 MR. FROST: Objection to 10 form. 11 THE WITNESS: Yeah, could 12 you repeat that again. 13 BY MR. SMITH: 14 Q. Tremolite, anthophyllite, 15 and actinolite. 16 A. And the -- 17 MR. FROST: Objection to 18 form. 19 THE WITNESS: Are you -- 20 yeah, are you saying that the 21 asbestos varieties of these have 22 been found in Baby Powder? 23 BY MR. SMITH: 24 Q. Yes, ma'am.</p>
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<p>1 THE WITNESS: Yeah, that 2 would be great. 3 MR. FROST: Do you mind if I 4 point to where you were? 5 MR. SMITH: Oh, yeah. No, 6 no, no. 7 THE WITNESS: I'm just -- 8 I'm looking at this. Okay. 9 BY MR. SMITH: 10 Q. Do you see that, Doctor, in 11 the footnote? 12 A. Yes. 13 Q. Okay. 14 (Whereupon, a discussion was 15 held off the stenographic record.) 16 BY MR. SMITH: 17 Q. All right, Doctor, different 18 types of asbestos vary in potency as 19 carcinogens; however, they're all 20 recognized as carcinogens, right? 21 A. Yes. In animals, yes. 22 Q. And I asked you this 23 earlier. Do you know the types of 24 asbestos that were found either</p>	<p>1 MR. FROST: Objection to 2 form. 3 THE WITNESS: Okay. 4 BY MR. SMITH: 5 Q. And you haven't seen the 6 internal documents of Johnson &amp; Johnson 7 regarding this matter, have you? 8 A. I haven't. 9 Q. And you haven't seen the 10 internal documents of Imerys or Luzenac, 11 have you, on this? 12 A. That's correct. 13 Q. And you have not seen the 14 reports of Dr. Longo and Rigler, correct? 15 A. Correct. 16 MR. SMITH: What is the 17 geologist's name? 18 BY MR. SMITH: 19 Q. And you haven't seen the 20 geologist expert Cook, Dr. Cook in this 21 case, you haven't seen his report, have 22 you? 23 A. I might have scanned his 24 report, but I don't recall it</p>

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<p style="text-align: right;">Page 202</p> <p>1 specifically.</p> <p>2 Q. Okay. Have you -- we'll get</p> <p>3 back to that in a minute.</p> <p>4 Your personal research has</p> <p>5 not dealt with tremolite asbestos,</p> <p>6 correct?</p> <p>7 A. No. I've only looked at</p> <p>8 tremolite in its non-asbestos form.</p> <p>9 Q. Your personal research has</p> <p>10 not dealt with tremolite asbestos,</p> <p>11 correct?</p> <p>12 MR. FROST: Objection to</p> <p>13 form.</p> <p>14 THE WITNESS: Yeah. I've</p> <p>15 looked at tremolite, but not the</p> <p>16 asbestos. That's correct.</p> <p>17 BY MR. SMITH:</p> <p>18 Q. Your personal research has</p> <p>19 not dealt with anthophyllite asbestos,</p> <p>20 correct?</p> <p>21 A. I have not used</p> <p>22 anthophyllite, that's correct.</p> <p>23 Q. Your personal research has</p> <p>24 not dealt with actinolite asbestos,</p>	<p style="text-align: right;">Page 204</p> <p>1 Q. Yours did too?</p> <p>2 A. Yeah.</p> <p>3 Q. Wasn't a very good job of</p> <p>4 binding that, was it?</p> <p>5 Bear with me just a second.</p> <p>6 And to your knowledge there are no</p> <p>7 detailed studies comparing the chemistry</p> <p>8 of tremolite asbestos to tremolite</p> <p>9 cleavage fragments, correct?</p> <p>10 A. That would be a question</p> <p>11 that should be posed to a geologist. I</p> <p>12 have not looked at the mineralogy</p> <p>13 literature for those comparisons.</p> <p>14 Q. With regard to anthophyllite</p> <p>15 asbestos and anthophyllite cleavage</p> <p>16 fragments, you have not studied the</p> <p>17 differences in chemistry between the two,</p> <p>18 correct?</p> <p>19 A. That's correct.</p> <p>20 Q. And the same with regard to</p> <p>21 actinolite asbestos and actinolite --</p> <p>22 actinolite cleavage fragments?</p> <p>23 A. That's correct.</p> <p>24 Q. And aside from the one study</p>
<p style="text-align: right;">Page 203</p> <p>1 correct?</p> <p>2 A. That's correct.</p> <p>3 Q. You cannot tell me how</p> <p>4 carcinogenic or potent tremolite or</p> <p>5 anthophyllite are, correct?</p> <p>6 MR. FROST: Objection to</p> <p>7 form.</p> <p>8 THE WITNESS: Again, I can</p> <p>9 tell you based on the epidemiology</p> <p>10 that anthophyllite is a weak agent</p> <p>11 in the development of</p> <p>12 mesotheliomas as compared to</p> <p>13 crocidolite or amosite asbestos.</p> <p>14 BY MR. SMITH:</p> <p>15 Q. You have never studied the</p> <p>16 differences between tremolite asbestos</p> <p>17 and tremolite cleavage fragments,</p> <p>18 correct?</p> <p>19 A. I haven't used the two</p> <p>20 comparatively in experiments, that's</p> <p>21 correct.</p> <p>22 Q. This thing fell apart.</p> <p>23 That's crazy.</p> <p>24 A. Mine fell apart too.</p>	<p style="text-align: right;">Page 205</p> <p>1 in upstate New York on talc, you've never</p> <p>2 studied tremolite or anthophyllite</p> <p>3 cleavage fragments yourself, correct?</p> <p>4 A. The study that I performed</p> <p>5 was with Dr. Wiley.</p> <p>6 Q. Aside from the one study in</p> <p>7 upstate New York on talc, you have never</p> <p>8 studied tremolite or anthophyllite</p> <p>9 cleavage fragments yourself, have you?</p> <p>10 MR. FROST: Objection to</p> <p>11 form.</p> <p>12 THE WITNESS: Correct. It's</p> <p>13 just that one study.</p> <p>14 BY MR. SMITH:</p> <p>15 Q. And the talc in your New</p> <p>16 York study that we just discussed was</p> <p>17 a -- an industrial grade talc and not</p> <p>18 cosmetic-grade talc; is that correct?</p> <p>19 A. Yes. There were three</p> <p>20 samples of talc with various proportions</p> <p>21 of fibers.</p> <p>22 Q. You have not studied how</p> <p>23 tremolite, anthophyllite, and actinolite</p> <p>24 asbestos reached the areas of the lungs</p>

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<p>1 where meso is induced and developed, and 2 you cannot make a strict analogy to these 3 types of asbestos from your study of 4 other types of asbestos; is that correct? 5 MR. FROST: Objection to 6 form. 7 THE WITNESS: Yeah, I -- I'd 8 have to ask someone who is an 9 expert in dosimetry. Assuming 10 that dimensions of fibers govern 11 where they end up in the lung, the 12 results that we have may be 13 relevant certainly to these types 14 of materials. 15 BY MR. SMITH: 16 Q. Okay. I'm going to ask the 17 question again. I don't think it was 18 responsive. 19 You have studied -- you have 20 not studied how tremolite, anthophyllite, 21 and actinolite asbestos reached the area 22 in the lungs where meso is induced and 23 developed, correct? 24 MR. FROST: Objection to</p>	<p>1 In the -- it's broken up. 2 Whatever. 3 MR. FROST: Mine stayed 4 together. 5 THE WITNESS: Yeah, mine is 6 broken, so... 7 MR. FROST: 179 you said? 8 MR. SMITH: Yes, please. 9 MR. FROST: Here, do you 10 want -- do you want to switch, 11 Brooke? 12 THE WITNESS: That's okay. 13 MR. FROST: Mine is still 14 bound. So do you want to switch? 15 THE WITNESS: I think I'm 16 prime viewing here. 17 No, just in different 18 pieces. 179. 19 Okay. 20 BY MR. SMITH: 21 Q. All right. On Line 11: 22 "And then you were asked the following 23 question: 24 "Okay. Well, I think the</p>
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<p>1 form. 2 THE WITNESS: I -- yeah, I 3 have not studied those three 4 materials in inhalation 5 experiments. 6 BY MR. SMITH: 7 Q. And you cannot make a strict 8 analogy as to these types of asbestos 9 from your other study -- from your study 10 of other types of asbestos; is that 11 correct? 12 MR. FROST: Objection to 13 form. 14 THE WITNESS: And -- and my 15 comment was that if they are of 16 the same dimensional 17 characteristics of the materials 18 that I use, namely crocidolite 19 asbestos, I could make some 20 analogies based upon their size 21 and fiber characteristics. 22 BY MR. SMITH: 23 Q. Okay. The -- I want you to 24 go to Page 179 in Leavitt, please.</p>	<p>1 record will speak for itself, but I think 2 you did give that in your answer when I 3 asked you. Let me ask you generally. 4 "This whole set of opinions 5 regarding how minerals such as asbestos 6 get to sites where mesothelioma is 7 induced and developed, does that apply to 8 tremolite, actinolite, and 9 anthophyllite?" 10 "And your answer: I don't 11 know. These, again, the animal studies 12 have been done with short and long 13 amosite asbestos and they have been done 14 with crocidolite asbestos. And the 15 groups that have done these experiments 16 have not looked at tremolite and 17 actinolite or anthophyllite because they 18 are the least potent types of asbestos. 19 So I can't make a strict analogy between 20 what's been studied and the asbestos 21 types that I" -- "that haven't been 22 studied." 23 "Did I read that correctly? 24 "And your answer was that's</p>

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<p>1 correct."</p> <p>2 Can I rely on that</p> <p>3 testimony?</p> <p>4 A. You -- you can.</p> <p>5 Q. Okay. You have not studied</p> <p>6 the bio durability of asbestos cleavage</p> <p>7 fragments or talc in any human tissue,</p> <p>8 correct?</p> <p>9 A. I have not looked at tissue</p> <p>10 digestion studies, that's correct.</p> <p>11 Q. You have not performed any</p> <p>12 studies on whether cleavage fragments can</p> <p>13 reach the area of the lung where meso</p> <p>14 is -- mesothelioma is induced and</p> <p>15 develops, correct?</p> <p>16 A. I have not done inhalation</p> <p>17 studies with cleavage fragments.</p> <p>18 Q. And you have not performed</p> <p>19 any studies on whether cleavage fragments</p> <p>20 can reach the area of the lung -- excuse</p> <p>21 me, reach the area -- excuse me. Let me</p> <p>22 back up. I'm going to get it right here</p> <p>23 in a second.</p> <p>24 You have not performed any</p>	<p>1 cleavage fragment as opposed to the</p> <p>2 asbestos fiber is beyond the scope of</p> <p>3 your expertise, correct?"</p> <p>4 And your answer under</p> <p>5 that -- under oath at that time was, "I</p> <p>6 do not do the measurements, no.</p> <p>7 That's" -- "that's correct."</p> <p>8 Is that true?</p> <p>9 A. No, actually, I have done</p> <p>10 the measurements with Dr. Woodworth on</p> <p>11 preparations of cleavage fragments and</p> <p>12 the respective asbestos fiber</p> <p>13 preparations, and that was done in the</p> <p>14 1980s and '90s.</p> <p>15 Q. So this was just a</p> <p>16 misstatement in Leavitt?</p> <p>17 MR. FROST: Objection to</p> <p>18 form.</p> <p>19 THE WITNESS: Yeah, I don't</p> <p>20 think it was a misstatement. I --</p> <p>21 I say, "I don't do the</p> <p>22 measurements in each experiment.</p> <p>23 I have in the past."</p> <p>24 So that's what I was</p>
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<p>1 studies on whether talc can reach the</p> <p>2 area of the ovaries which can lead to</p> <p>3 ovarian cancer, correct?</p> <p>4 A. I have not studied migration</p> <p>5 of talc.</p> <p>6 Q. Distinguishing the</p> <p>7 dimensions, the aspect ratio of a</p> <p>8 cleavage fragment as opposed to an</p> <p>9 asbestos fiber is beyond the scope of</p> <p>10 your expertise, correct?</p> <p>11 A. I have done some work on</p> <p>12 dimensional characteristics in the 1980s,</p> <p>13 where we compared cleavage fragment</p> <p>14 population to asbestos fibers and those</p> <p>15 are papers by Woodworth, et al., and</p> <p>16 Hansen, et al., in cancer research.</p> <p>17 Q. Okay. Can you go to 193 of</p> <p>18 the Leavitt testimony, please?</p> <p>19 A. Okay.</p> <p>20 Q. And it's down on page -- I</p> <p>21 mean, excuse me, Line 23.</p> <p>22 "Question" -- and you were</p> <p>23 asked, "Simply put, distinguishing the</p> <p>24 dimensions, the aspect ratio of the</p>	<p>1 referring to. That's in the next</p> <p>2 six to eight lines on 194.</p> <p>3 BY MR. SMITH:</p> <p>4 Q. And then you continue on by,</p> <p>5 "Now I give it to a -- someone in our</p> <p>6 cell imaging facility," correct?</p> <p>7 A. Right. We have people who</p> <p>8 do those measurements.</p> <p>9 Q. Okay. You've never measured</p> <p>10 the flexibility or tensile strength of</p> <p>11 asbestos or cleavage fragments, correct?</p> <p>12 A. That's correct. I don't</p> <p>13 measure flexibility.</p> <p>14 Q. Flexibility of asbestos</p> <p>15 fiber within a lung cell causing</p> <p>16 mechanical injury is just a hypothesis,</p> <p>17 correct?</p> <p>18 A. Well -- well, it --</p> <p>19 MR. FROST: Objection to</p> <p>20 form.</p> <p>21 THE WITNESS: Yeah, it was</p> <p>22 originally hypothesized by someone</p> <p>23 named Archer who looked at plastic</p> <p>24 films and measured the amount of</p>



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<p style="text-align: right;">Page 214</p> <p>1 free radical generation and 2 flexibility. So I think it's more 3 than a hypothesis. It's been 4 proven by some experimental data. 5 BY MR. SMITH: 6 Q. Go to Page 172 in your 7 Leavitt testimony. 8 A. Okay. 9 Q. And I'm -- I'm going to 10 hopefully maybe get you a better copy or 11 something. 12 A. It's okay. We're getting 13 there. 14 Q. All right. 172. Line 15. 15 "Okay. When" -- "when asked 16 about flexibility you said in the past 17 there is a hypothesis that the 18 flexibility of an asbestos fiber within 19 the lung within a cell can cause 20 mechanical injury, correct? 21 "Yeah" -- and your answer 22 was, "Yes." 23 "Question: Okay. But 24 that's a hypothesis, correct?"</p>	<p style="text-align: right;">Page 216</p> <p>1 THE WITNESS: Want to take a 2 short -- 3 MR. FROST: Yeah, so why 4 don't we take like a five-minute 5 break and then -- I mean, I'm 6 generally fine going through 7 lunch. I don't normally take 8 lunches, but if the witness if 9 fine and you're fine -- 10 MS. O'DELL: What's your 11 preference though? 12 THE WITNESS: It -- it's up 13 to you. I'd just as soon go. 14 MR. SMITH: Well, we're 15 going to have a -- 16 MS. O'DELL: I think we 17 should have lunch at some point. 18 MR. SMITH: I'm going to 19 have to eat something. 20 THE WITNESS: Okay. 21 MR. FROST: Okay. How long 22 is your next section? Is it like 23 half an hour, 45 minutes? 24 MR. SMITH: That's a good</p>
<p style="text-align: right;">Page 215</p> <p>1 And your answer was what? 2 A. My answer was, "Yes." But 3 as I just stated, there have been studies 4 showing that flexibility within a cell 5 can cause oxidants that then are 6 associated with a mechanical injury. 7 So this statement is -- is 8 correct, but I think my statement in 9 terms of Archer experiments, it -- also 10 relate to flexibility and things that 11 injure cells. 12 Q. Is your -- can I rely on 13 your answer in Leavitt right there? 14 A. Sure. 15 MR. SMITH: Okay. I'm 16 getting ready to move to a 17 different section. Are we 18 breaking for lunch, are we just 19 going to plow through? What do 20 you want to do? 21 THE WITNESS: Let's go 22 through. 23 MR. FROST: Yeah, I was 24 going to say --</p>	<p style="text-align: right;">Page 217</p> <p>1 question. I think we probably 2 better break now. 3 MR. FROST: You want to 4 break now? 5 MR. SMITH: Yeah. 6 THE WITNESS: Okay. 7 MR. SMITH: Is that okay? 8 THE WITNESS: Sure. 9 MR. FROST: Yeah, that's 10 fine. 11 THE VIDEOGRAPHER: Going off 12 record. The time is 12:16. 13 - - - 14 (Lunch break.) 15 - - - 16 A F T E R N O O N S E S S I O N 17 - - - 18 THE VIDEOGRAPHER: We are 19 going back on record beginning 20 Media File Number 3. The time is 21 1:22. 22 - - - 23 EXAMINATION (Cont'd.) 24 - - -</p>

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<p>1 BY MR. SMITH: 2 Q. All right. Doctor, we just 3 took a lunch break, and I just have some 4 more questioning for you. 5 In your paper -- excuse me, 6 in your report for the MDL, you state, on 7 Page 10, under Paragraph D, "Chronic 8 inflammation and foreign body 9 carcinogenesis." And I quote, "Chronic 10 inflammation over months and years can 11 result in many diseases, including 12 cancers, but has not been established as 13 a cause of ovarian cancer, and there is 14 evidence that is difficult to reconcile 15 with the inflammation hypothesis." And 16 you have Ni cited. 17 And then you go on to say, 18 "The relationship between cancer and 19 inflammation is not simple and cannot be 20 reduced to one grand theory," quoting 21 Rakoff-Nahoum, 2006. Do you recall that 22 in your report? 23 A. Yes. Do you -- 24 MR. FROST: So yeah, I was</p>	<p>1 "Chronic inflammation and foreign body 2 carcinogenesis." 3 A. Yes. 4 Q. Did I read that correctly? 5 It's the -- it's six lines down starting 6 with, "Chronic inflammation," to the 7 right. I'll read it again. 8 A. Yes. 9 Q. "Chronic inflammation over 10 months and years can result in many 11 diseases including cancers but has not 12 been established as a cause of ovarian 13 cancer, and there is evidence that is 14 difficult to reconcile with the 15 inflammation hypothesis." You cite Ni, 16 et al., 2012. 17 "Notably Rakoff-Nahoum, 18 2006, cautions, 'The relationship between 19 cancer and inflammation is not simple and 20 cannot be reduced to one grand theory.' 21 Did I read that correctly? 22 A. You did. 23 Q. Okay. And this is in your 24 MDL report as part of your opinion in</p>
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<p>1 going to say, can we mark a copy 2 of the report? It might make it 3 easier. 4 MR. SMITH: Sure. I have 5 some copies. 6 (Document marked for 7 identification as Exhibit 8 Mossman-21.) 9 BY MR. SMITH: 10 Q. I'm going to mark a clean 11 copy. 12 MR. SMITH: Can I keep one 13 of them? 14 MR. FROST: Sure. I was 15 going to say, is one marked up? 16 MR. SMITH: Yeah. 17 BY MR. SMITH: 18 Q. And that would be the next 19 numbered exhibit, Exhibit 21. And, 20 Doctor, I was reading on Page 10 of your 21 report. 22 A. Okay. 23 Q. From Page 10 of your report. 24 Right in that first paragraph under,</p>	<p>1 this case, correct? 2 A. It is. 3 MR. SMITH: I'm going to try 4 to make this as easy as possible. 5 But I put together -- it's a 6 two-sided document. 7 I'm going to mark it as the 8 next exhibit. It's going to be 9 12. And I created this. 10 MR. FROST: Object for the 11 record the use to compiled, 12 created. This is two pages? We 13 only have one. 14 But to finish my objection, 15 but yeah, I object to the use of, 16 you know, exhibits that you 17 created. 18 MR. SMITH: There should be 19 a back and front. 20 MR. FROST: That's what I 21 figured. Yeah, it's just the -- 22 THE WITNESS: It's just Page 23 1. 24 MR. SMITH: All right.</p>

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<p>1 Well, let's do this. I'm going to 2 mark -- and we'll go through it. 3 I'm going to have to probably do 4 it back on the Elmo because I 5 don't know what happened. They 6 copied this downstairs. I 7 don't -- I don't have an 8 explanation. 9 I'm going to mark, which is 10 the back and front, which you just 11 have the front, as Exhibit 24. 12 And then when we get to the back 13 of it, I'm going to have to use 14 the Elmo. 15 (Document marked for 16 identification as Exhibit 17 Mossman-24.) 18 BY MR. SMITH: 19 Q. I just want to go through 20 these studies. And just walk through 21 them with you and ask you some questions. 22 They're quotes from these different 23 studies. And first let me ask you. 24 Let's go to the first one.</p>	<p>1 No. I actually scanned it because 2 it was presented to me in another 3 matter while on the stand. So I 4 did not look at it in detail. 5 BY MR. SMITH: 6 Q. Okay. So you've not read 7 this back to front, this draft screening 8 assessment from Health Canada? 9 A. That's -- that's correct. 10 Q. You were just asked 11 questions about certain parts of it on 12 the stand, witness stand? 13 A. I was. 14 Q. Okay. Was that in the 15 Leavitt case? 16 A. I believe so, yes. 17 Q. Second quote from this draft 18 screening assessment on this page: 19 "There is support for an association of 20 inflammation and increased risk of 21 ovarian cancer." 22 Would you agree or disagree 23 with that statement? 24 MR. FROST: Objection to</p>
Page 223	Page 225
<p>1 The draft screening 2 assessment "Talc, Environment, and 3 Climate Change," Canada, Health Canada 4 December 2018. Did you use that as part 5 of your reliance materials for your 6 opinion in this case? 7 A. I did not. 8 Q. Okay. And it says, "With 9 respect to talc specifically, local 10 irritation leading to an inflammatory 11 response is one of the possible 12 mechanisms of tumor progression that is 13 frequently hypothesized." 14 You've not read the Health 15 Canada draft screening assessment 16 referenced here? 17 A. I have scanned it, yes. 18 Q. You just said you hadn't 19 seen it. Now you say you scanned it. 20 Which is it? 21 MR. FROST: Objection to 22 form. 23 THE WITNESS: You asked me 24 if I read it in its completeness.</p>	<p>1 form. 2 THE WITNESS: I would 3 disagree with both of them. 4 Although I think the first one 5 states possible and hypothesis. 6 And again local irritation is a 7 hypothesis. But I would disagree 8 with both of them. 9 BY MR. SMITH: 10 Q. And the -- the second -- the 11 third paragraph down cites the second 12 article -- a second article, Taher. Have 13 you read Taher in reliance of your 14 opinions in this case? 15 A. No, I see this is an 16 unpublished document. 17 Q. Well, it is an unpublished 18 document that's been published. It's in 19 peer-reviewed literature. 20 Taher, you've never read it? 21 MR. FROST: Objection to 22 form. 23 THE WITNESS: Yeah. I am 24 unaware of it. And if it has been</p>

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<p>1 published in the peer-review 2 literature, it hasn't appeared on 3 my searches. 4 MR. SMITH: And that is -- 5 I'm going to mark this as 6 Exhibit 22. 7 Is that correct? 8 (Document marked for 9 identification as Exhibit 10 Mossman-22.) 11 MS. O'DELL: This is 24. 12 MR. SMITH: Oh my gosh. 13 MS. O'DELL: We didn't do a 14 20 -- 15 MR. FROST: Oh, I see. 16 Okay. 17 MR. SMITH: Does it really 18 matter? 19 MR. FROST: I was going to 20 say we can do 22. I don't think 21 it has been -- 22 MR. MIZGALA: So this, this 23 is 24? 24 MR. SMITH: Yeah, this is</p>	<p>1 inflammation in local immunogenicity has 2 been linked to causation of ovarian 3 cancers in anything that I've read. 4 Q. But you haven't read Taher? 5 A. No. This is an unpublished 6 document. I'm not sure where it's 7 published. 8 I haven't seen this document 9 and certainly I never saw it before my 10 report. So I would wonder what's new 11 about it and what's the source. I don't 12 know of any of the authors and haven't 13 heard of them as well. So I couldn't 14 really comment on this. 15 Q. You don't know -- have any 16 knowledge about whether this 17 meta-analysis was produced and submitted 18 to Health Canada for their risk 19 assessment of talc not containing 20 asbestos? 21 A. No, it -- 22 MR. FROST: Objection to 23 form. 24 BY MR. SMITH:</p>
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<p>1 24 -- 2 MR. FROST: So I think this 3 one will be 22. 4 MR. SMITH: It doesn't 5 matter what number. 6 MR. FROST: We can use 22 7 and 23 now. 8 MR. SMITH: Yeah. Okay. 9 BY MR. SMITH: 10 Q. This is a systematic review 11 of the meta-analysis of the association 12 between perineal use of talc and risk of 13 ovarian cancer. Have you read and relied 14 on this study in support of your opinion 15 in this case? 16 A. I have not seen this study 17 before. 18 Q. Okay. And the quote on 19 Page 26, "Chronic inflammatory response 20 and alteration in local immunogenicity 21 are possible mechanisms." 22 Would you agree with that, 23 as far as mechanisms for ovarian cancer? 24 A. I don't think that chronic</p>	<p>1 Q. Okay. 2 A. It's not in the 3 peer-reviewed literature. And I'm 4 unfamiliar with Dr. Taher or any of the 5 other authors in terms of their 6 contributions to the field. 7 Q. Next is a -- a study called 8 Penninkilampi 2018. You referenced that 9 earlier. 10 Did you rely on the 11 Penninkilampi study for the basis of any 12 of your opinions in this case? 13 A. Yes. But I emphasize that 14 this was a meta-analysis and a -- an 15 epidemiological study that didn't look 16 as -- at the quote as any foreign bodies. 17 And so I wouldn't agree with this 18 statement. 19 I don't think that there is 20 any information in this article or in 21 other ones that talc would ascend 22 perineally to the ovary. 23 Q. Quote, if chronic -- and I'm 24 quoting Penninkilampi. If chronic</p>

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<p style="text-align: right;">Page 230</p> <p>1 inflammation due to ascending foreign 2 bodies is indeed the mechanism by which 3 talc is associated with increased ovarian 4 cancer, then these revoked results fit 5 the picture. And you said that you don't 6 believe that talc can ascend through the 7 fallopian tubes to the ovaries; is that 8 correct? 9 A. And I'm -- 10 Q. And we'll get to that in a 11 minute about migration. 12 MR. FROST: Objection to 13 form. 14 THE WITNESS: Yeah, I think 15 that this -- the question if is 16 indeed the mechanism is unproven. 17 And certainly not in the 18 Penninkilampi epidemiological 19 meta-analysis. 20 BY MR. SMITH: 21 Q. Have you read the Trabert, 22 Pinto and Hartge, et al., 2014 document 23 and used that as a basis of your opinions 24 in this case?</p>	<p style="text-align: right;">Page 232</p> <p>1 But as I remember this statement, 2 it was referenced to a hypothesis 3 paper by Ness and -- I believe it 4 was Cottreau in 1999 or 2000. And 5 that was the reference for this 6 statement. Certainly not the 7 paper which I believe was looking 8 at systemic markers of 9 inflammation and not ovarian 10 related markers in the ovary. 11 BY MR. SMITH: 12 Q. There's another quote from 13 the Trabert study. "Our studies provide 14 additional evidence that inflammation 15 plays an important role in ovarian 16 carcinogenesis." 17 Would you agree or disagree 18 with that statement from Trabert? 19 MR. FROST: Objection to 20 form. 21 THE WITNESS: Again, I don't 22 have the paper in front of me, but 23 Trabert did not look at localized 24 inflammation in the ovary. I</p>
<p style="text-align: right;">Page 231</p> <p>1 A. I have. 2 Q. And quote from that study, 3 "Epidemiologic evidence implicates 4 chronic inflammation as a central 5 mechanism in the pathogenesis of ovarian 6 cancer." 7 What's pathogenesis means? 8 A. Pathogenesis means the 9 development of disease. So it could be 10 any -- it could be talking about anything 11 from causation to later stages of 12 disease. 13 Q. Well, here, "Epidemiologic 14 evidence implicates chronic inflammation 15 as a central mechanism in the 16 pathogenesis of ovarian cancer, the most 17 lethal gynecologic cancer among women in 18 the United States." 19 Would you agree or disagree 20 with that statement from Trabert? 21 MR. FROST: Objection to 22 form. 23 THE WITNESS: Yeah, I would 24 have to look at the Trabert paper.</p>	<p style="text-align: right;">Page 233</p> <p>1 believe this was a study where 2 they looked at a total of over 40 3 markers of inflammation and found 4 only two systemically in 5 individuals with preexisting 6 cancer. 7 So, if it does play a role 8 in ovarian carcinogenesis, it 9 certainly is very speculative with 10 regard to causation. 11 BY MR. SMITH: 12 Q. Well, it doesn't seem 13 speculative here. The quote states: 14 "Our study provides additional 15 evidence" -- "provides additional 16 evidence that inflammation plays an 17 important role in ovarian 18 carcinogenesis." 19 It's pretty direct there. 20 It doesn't say anything about hypothesis 21 or -- or any of the qualifiers that 22 you're saying, Doctor, does it? 23 MR. FROST: Objection to 24 form.</p>

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<p>1 THE WITNESS: Yeah, let me 2 emphasize though, here they are 3 looking at systemic markers of 4 inflammation in the serum of 5 patients, and some of the markers 6 they found are the same ones that 7 have been detected in lung cancers 8 or in other models of cancer. 9 So whether inflammation 10 plays a critical role is 11 speculative. 12 BY MR. SMITH: 13 Q. They didn't say it was 14 speculative? 15 MR. FROST: Objection to 16 form. 17 BY MR. SMITH: 18 Q. Correct? 19 A. They did not look at 20 inflammation in the ovary. So you can't 21 equate systemic inflammatory markers with 22 causative roles in disease especially if 23 you're looking at individuals who had 24 disease.</p>	<p>1 Would you agree or disagree 2 with that statement? 3 MR. FROST: Objection to 4 form. 5 THE WITNESS: I would 6 disagree that his studies 7 illustrated that endometriosis is 8 linked to the risk of ovarian 9 cancer. Other studies have shown 10 that it's not. 11 BY MR. SMITH: 12 Q. Have you relied on Merritt 13 2008 as a basis for your opinions in this 14 case? 15 A. Again, I'd have to go back 16 and -- did I list this in my references? 17 Then I could tell you. 18 Q. Well, let's look. 19 THE WITNESS: Do we have the 20 references? 21 MR. FROST: The references 22 aren't attached. 23 THE WITNESS: Yeah. 24 MR. SMITH: Hold on. I</p>
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<p>1 MR. FROST: And she said it 2 in her answer. I was trying to 3 get it in before. I want to lodge 4 the general objection that I think 5 it's improper to be asking her 6 about questions about papers that 7 aren't in front of her. 8 BY MR. SMITH: 9 Q. Did you look at the Wu 2009 10 paper? 11 A. I did, and again, this is an 12 epidemiology paper. I'd have to look at 13 it again to see where the source of this 14 statement comes from, whether it's 15 reference to another study or whether 16 he's talking about specific things here 17 such as talc and endometriosis that he's 18 identified as variables. 19 Q. Quote, "Our findings on talc 20 and endometriosis are consistent with 21 previous findings and compatible with the 22 hypothesis that these factors increase 23 the risk of ovarian cancer and that 24 inflammation may be a common pathway."</p>	<p>1 should have it. 2 (Document marked for 3 identification as Exhibit 4 Mossman-23.) 5 BY MR. SMITH: 6 Q. Is Merritt 2008 one of the 7 studies that you relied on in the basis 8 of your opinions in this case? 9 A. Let me just look at it just 10 to make sure. 11 Q. I can't remember if I 12 attached that reference. 13 A. No. 14 Q. I did your updated, but I'm 15 going to attach this as Exhibit 23, the 16 original key references and reliance 17 materials. I attached the amended one 18 earlier. 19 Doctor? 20 A. Yes. 21 Q. Did you rely on Merritt to 22 form the basis of your opinions in this 23 case? 24 A. No, I did not.</p>

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<p style="text-align: right;">Page 238</p> <p>1 Q. And from that paper, quote, 2 "Chronic inflammation has been proposed 3 as a possible causal mechanism that 4 explains the observed association between 5 certain risk factors, such as the use of 6 talcum powder, talc, in the pelvic region 7 and epithelial ovarian cancer." 8 Would you agree or disagree 9 with that statement from Merritt? 10 MR. FROST: Objection. 11 THE WITNESS: I'd have to 12 see the paper to see in which 13 context it was used and also what 14 reference was supplied. 15 Again, I think the key word 16 here is "possible." So I'm not 17 aware that this paper presented 18 any causative role or causative 19 link between talcum powder and 20 ovarian cancer. 21 BY MR. SMITH: 22 Q. Well, do you -- are you of 23 the opinion that chronic inflammation is 24 a possible causal mechanism to ovarian</p>	<p style="text-align: right;">Page 240</p> <p>1 only one, I think, compelling 2 study that indicates that chronic 3 inflammation is not a causal 4 mechanism. Let me emphasize that 5 I also have looked at the 6 meta-analysis on pelvic 7 inflammatory disease that show 8 that this is not linked to ovarian 9 cancer, as well as the data on 10 aspirin and NSAIDs. 11 BY MR. SMITH: 12 Q. That wasn't -- my question 13 wasn't about whether it shows a causal 14 relationship. My question is, to you, 15 are you of the opinion chronic 16 inflammation is a possible mechanism 17 leading to the development of ovarian 18 cancer? 19 MR. FROST: Objection to 20 form. 21 THE WITNESS: Well, yeah, 22 and as I said previously, the data 23 suggests that it is not a possible 24 mechanism that leads to the</p>
<p style="text-align: right;">Page 239</p> <p>1 cancer? 2 MR. FROST: Objection to 3 form. 4 THE WITNESS: I would argue 5 against that based upon the 6 literature that I reviewed. We 7 can go into that later or we can 8 go into it now. 9 BY MR. SMITH: 10 Q. I'm just asking, do you 11 think chronic inflammation is a possible 12 mechanism leading to the development of 13 ovarian cancer? 14 A. Not based upon what I've 15 read or seen regarding Dr. Shih's work in 16 this regard. 17 Q. Dr. Shih's work? Is that 18 the basis of your opinion that chronic 19 inflammation is not a possible mechanism 20 leading to the development of ovarian 21 cancer? 22 MR. FROST: Objection to 23 form. 24 THE WITNESS: No, that's</p>	<p style="text-align: right;">Page 241</p> <p>1 development of disease. 2 BY MR. SMITH: 3 Q. Quote -- the next quote -- 4 And you say that the data 5 suggest that. What data are you talking 6 about? What work? Is this an expert 7 report? Is Shih an expert report? 8 MR. FROST: Objection to 9 form. 10 THE WITNESS: No. As I 11 said, the Shih study is only one 12 of many studies beginning at the 13 cell level, indicating in my own 14 work that talc does not give rise 15 to genes that induce chronic 16 inflammation. 17 Also the studies in animals 18 indicate that there is no chronic 19 inflammation associated with 20 disease development. 21 The pelvic inflammatory 22 disease literature and the 23 literature on aspirin and NSAIDs, 24 Dr. Shih's study examines this</p>

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<p>1 directly and is compelling</p> <p>2 evidence that chronic inflammation</p> <p>3 does not lead to the causation of</p> <p>4 ovarian cancers.</p> <p>5 BY MR. SMITH:</p> <p>6 Q. Where -- I'm looking on your</p> <p>7 reliance materials. Where is</p> <p>8 Dr. Shih's -- where is Dr. Shih listed on</p> <p>9 here?</p> <p>10 A. Dr. Shih's study was one</p> <p>11 that I read after I compiled my opinions;</p> <p>12 that is, my final report in this case.</p> <p>13 Q. When did you read that?</p> <p>14 A. I read that within the last</p> <p>15 two weeks.</p> <p>16 Q. Well, you provided me an</p> <p>17 updated list of materials relied upon.</p> <p>18 It's not in that.</p> <p>19 A. It should have been.</p> <p>20 Q. Is it?</p> <p>21 A. Yes.</p> <p>22 MR. FROST: It should be.</p> <p>23 BY MR. SMITH:</p> <p>24 Q. I see. It says "Expert</p>	<p>1 And yes, it is a compelling study</p> <p>2 showing that there is no</p> <p>3 inflammation associated with early</p> <p>4 lesions in ovarian cancers.</p> <p>5 BY MR. SMITH:</p> <p>6 Q. It's not a study, ma'am.</p> <p>7 It's an expert report. It's not peer</p> <p>8 reviewed, correct?</p> <p>9 MR. FROST: Objection.</p> <p>10 THE WITNESS: I'm sorry. As</p> <p>11 a pathologist, I looked at that</p> <p>12 data. It should be a</p> <p>13 peer-reviewed report and maybe</p> <p>14 some day.</p> <p>15 But the fact is, it was</p> <p>16 beautifully done and it was</p> <p>17 compelling data showing that</p> <p>18 inflammation is not associated</p> <p>19 with early intraepithelial</p> <p>20 development in serous types of</p> <p>21 cancers.</p> <p>22 BY MR. SMITH:</p> <p>23 Q. Ma'am, one day I might be</p> <p>24 president of the United States.</p>
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<p>1 report of Shih."</p> <p>2 A. That's what I'm talking</p> <p>3 about.</p> <p>4 Q. That's a defense expert</p> <p>5 report?</p> <p>6 A. That's correct.</p> <p>7 Q. So one of the major bases of</p> <p>8 whether talc can cause chronic</p> <p>9 inflammation that could possibly lead to</p> <p>10 the development of ovarian cancer, one of</p> <p>11 your major reliance materials is an</p> <p>12 expert report for the defendants in this</p> <p>13 litigation?</p> <p>14 MR. FROST: Objection.</p> <p>15 THE WITNESS: That's not</p> <p>16 what I said.</p> <p>17 BY MR. SMITH:</p> <p>18 Q. You said it was a compelling</p> <p>19 study that you relied upon for that</p> <p>20 opinion.</p> <p>21 MR. FROST: Objection.</p> <p>22 THE WITNESS: It bolstered</p> <p>23 my preexisting opinions written in</p> <p>24 my report before I saw the study.</p>	<p>1 My question to you is, is</p> <p>2 that a peer-reviewed publication?</p> <p>3 MR. FROST: Objection to</p> <p>4 form.</p> <p>5 THE WITNESS: As I read it,</p> <p>6 no. But I'm sure it will be some</p> <p>7 day.</p> <p>8 BY MR. SMITH:</p> <p>9 Q. Okay. What do you base your</p> <p>10 opinion on, "I'm sure it will be some</p> <p>11 day"? What do you base that on?</p> <p>12 MR. FROST: Objection.</p> <p>13 THE WITNESS: Dr. Shih is an</p> <p>14 international expert in this</p> <p>15 field. A leading pathologist in</p> <p>16 this field. And, therefore, this</p> <p>17 study is at a high -- I would call</p> <p>18 it a highly ranked, thorough study</p> <p>19 done beautifully by leading</p> <p>20 pathologists in this field.</p> <p>21 BY MR. SMITH:</p> <p>22 Q. All those accolades gave</p> <p>23 by -- given by another defense expert</p> <p>24 being paid in this litigation, correct?</p>

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<p style="text-align: right;">Page 246</p> <p>1 MR. FROST: Objection to 2 form. 3 THE WITNESS: I am not 4 certain to whether how much he or 5 she is being paid. I'm not 6 looking at the report as a report, 7 per se. I'm looking at the data 8 and assessing it scientifically, 9 and it is compelling data. 10 BY MR. SMITH: 11 Q. I meant all the accolades 12 that you're throwing on this expert 13 report are by you, who is a defense paid 14 expert and been in talc litigation since 15 2014; is that correct, Dr. Mossman? 16 A. No, it's -- 17 MR. FROST: Objection -- 18 BY MR. SMITH: 19 Q. That's not correct? Let's 20 break it down then. 21 A. No, let -- let me finish. 22 Q. Okay. 23 A. I'm not talking as an expert 24 for defense in litigation. I'm talking</p>	<p style="text-align: right;">Page 248</p> <p>1 BY MR. SMITH: 2 Q. Studied the field of talc 3 and ovarian cancer for 40 years? 4 A. No. 5 MR. FROST: Objection. 6 THE WITNESS: Who studied 7 the field of ovarian cancer most 8 recently. But who has done 9 research on development of 10 epithelial cancers in the cervix, 11 in the skin, and in the lung. 12 BY MR. SMITH: 13 Q. That's not what we are 14 about. We're talking about ovarian 15 cancer. I'm not talking about the cervix 16 or the lung -- I'm not talking about 17 cervical cancer. 18 Do you understand that? I'm 19 talking about ovarian cancer. 20 MR. FROST: Objection to 21 form. 22 THE WITNESS: What I'm 23 saying is that inflammation is 24 inflammation regardless of the</p>
<p style="text-align: right;">Page 247</p> <p>1 as a pathologist in the study of science. 2 This was a scientific study, 3 and it was done correctly and it is very 4 important in terms of bolstering my 5 opinions which were linked to other 6 things prior to my seeing the Shih study. 7 Q. Ma'am, it's an expert 8 report. Your reliance materials have you 9 here as a paid expert for Johnson &amp; 10 Johnson who is a defendant in the 11 litigation. You've been paid for talc 12 litigation since 2014. So your opinions 13 and your reliance materials and your 14 opinion in this case is for litigation. 15 Do you not understand that? 16 MR. FROST: Objection to 17 form. 18 THE WITNESS: Yes. And I 19 think you are incorrect. My 20 opinions are not as expert in 21 litigation. 22 My opinions are as a 23 scientist who has studied this 24 field for 40 years.</p>	<p style="text-align: right;">Page 249</p> <p>1 cancer that you're talking about. 2 BY MR. SMITH: 3 Q. So inflammation is 4 inflammation. 5 A. What I'm saying here is that 6 there is no evidence that chronic 7 inflammation is associated with the 8 causation or early development of ovarian 9 cancers. 10 Q. You have not performed one 11 study on cosmetic-grade talc, correct? 12 A. I have said that before, 13 yes. 14 Q. You have not performed one 15 study on Shower to Shower or Baby Powder 16 which are the products at issue in this 17 case, correct? 18 MR. FROST: Objection to 19 form. 20 THE WITNESS: As I 21 emphasize, I have looked at 22 industrial talcs -- 23 BY MR. SMITH: 24 Q. No, ma'am. That's not</p>

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<p>1 responsive to my question.</p> <p>2 My question is, have you</p> <p>3 performed any studies on Baby Powder and</p> <p>4 Shower to Shower that are at issue in</p> <p>5 this litigation?</p> <p>6 MR. FROST: Objection to</p> <p>7 form.</p> <p>8 THE WITNESS: I have not</p> <p>9 myself performed studies.</p> <p>10 BY MR. SMITH:</p> <p>11 Q. And have you performed</p> <p>12 studies on the types of asbestos that</p> <p>13 experts have found and internal documents</p> <p>14 have revealed from Johnson &amp; Johnson and</p> <p>15 Imerys that are in Baby Powder and Shower</p> <p>16 to Shower?</p> <p>17 MR. FROST: Objection.</p> <p>18 THE WITNESS: Again, I've</p> <p>19 looked at talc, fibrous talc,</p> <p>20 which contained non-asbestiform</p> <p>21 tremolite. And I'm unaware of</p> <p>22 scientific data supporting the</p> <p>23 claims that tremolite,</p> <p>24 anthophyllite, or actinolite</p>	<p>1 ovarian cancer."</p> <p>2 Would you agree or disagree</p> <p>3 with that statement from Merritt?</p> <p>4 MR. FROST: Objection.</p> <p>5 THE WITNESS: I don't have</p> <p>6 it in front of me. I -- I really</p> <p>7 can't comment on it.</p> <p>8 BY MR. SMITH:</p> <p>9 Q. You can't comment on that</p> <p>10 quote, whether you agree with that</p> <p>11 statement or not?</p> <p>12 A. Which one was this now? The</p> <p>13 chronic inflammation again?</p> <p>14 Q. It's the second one.</p> <p>15 "Chronic inflammation was first invoked</p> <p>16 as a possible mechanism leading to the</p> <p>17 development of epithelial ovarian cancer</p> <p>18 to explain observed associations between</p> <p>19 certain factors such as talcum powder in</p> <p>20 the perineal region or pelvic</p> <p>21 inflammatory disease, PID, and a risk of</p> <p>22 ovarian cancer."</p> <p>23 Do you agree or disagree</p> <p>24 with that statement?</p>
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<p>1 asbestos are in talcs.</p> <p>2 MR. SMITH: Object to</p> <p>3 nonresponsiveness.</p> <p>4 BY MR. SMITH:</p> <p>5 Q. My question is, have you</p> <p>6 ever performed a study on the types of</p> <p>7 asbestos that we went through earlier</p> <p>8 that have been found in the internal</p> <p>9 documents of Johnson &amp; Johnson and Imerys</p> <p>10 that are in Baby Powder and Shower to</p> <p>11 Shower and by experts that have tested</p> <p>12 Baby Powder bottles?</p> <p>13 MR. FROST: Objection.</p> <p>14 THE WITNESS: I have not.</p> <p>15 BY MR. SMITH:</p> <p>16 Q. Okay. In the Merritt --</p> <p>17 another Merritt quote here. "Chronic</p> <p>18 inflammation was first invoked as a</p> <p>19 possible mechanism leading to the</p> <p>20 development of epithelial ovarian cancer</p> <p>21 to explain observed associations between</p> <p>22 certain factors such as talcum powder in</p> <p>23 the perineal region or pelvic</p> <p>24 inflammatory disease and the risk of</p>	<p>1 MR. FROST: Objection to</p> <p>2 form.</p> <p>3 THE WITNESS: I disagree</p> <p>4 with the statement.</p> <p>5 BY MR. SMITH:</p> <p>6 Q. Thank you.</p> <p>7 Next Merritt quote:</p> <p>8 "Indeed, the most consistent evidence</p> <p>9 linking inflammation with ovarian cancer</p> <p>10 comes from many reports that use of the</p> <p>11 talc in the perineal region increases</p> <p>12 ovarian cancer risk."</p> <p>13 Would you agree or disagree</p> <p>14 with that statement from Merritt?</p> <p>15 MR. FROST: Objection.</p> <p>16 THE WITNESS: Again, I'd</p> <p>17 have to see the report and see the</p> <p>18 references, but the references</p> <p>19 that I have reviewed suggest that</p> <p>20 this is not consistent evidence at</p> <p>21 all.</p> <p>22 BY MR. SMITH:</p> <p>23 Q. And have you read Gates or</p> <p>24 did you rely on Gates 2008 for the basis</p>

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<p>1 of your opinion in this case?</p> <p>2 A. It was one of the cohort</p> <p>3 studies I believe.</p> <p>4 Q. She has several.</p> <p>5 A. I'd have to see the</p> <p>6 publication.</p> <p>7 Do you have it?</p> <p>8 MR. FROST: Reliance list.</p> <p>9 Did you check your reliance list?</p> <p>10 THE WITNESS: I mean, I have</p> <p>11 to see the publication itself.</p> <p>12 MR. FROST: Sure.</p> <p>13 MR. SMITH: I'll get that at</p> <p>14 a break. Yeah, I'll get that at a</p> <p>15 break. Let me see if I can find</p> <p>16 it real quick. If not, I'll move</p> <p>17 on. I'll come back to it.</p> <p>18 BY MR. SMITH:</p> <p>19 Q. But, quote, "Talc particles</p> <p>20 can induce an inflammatory response in</p> <p>21 vivo which may be important" -- what's</p> <p>22 "in vivo" mean?</p> <p>23 A. It means in the body.</p> <p>24 Q. "Talc particles can induce</p>	<p>1 I believe that no normal ovarian</p> <p>2 cells treated with talc undergo</p> <p>3 increased cell proliferation,</p> <p>4 neoplastic transformation, and</p> <p>5 generation of reactive oxygen</p> <p>6 species.</p> <p>7 She may be referencing</p> <p>8 another study which -- by</p> <p>9 Buz'Zard, et al., that encompasses</p> <p>10 these ideas.</p> <p>11 BY MR. SMITH:</p> <p>12 Q. I'm -- going to have to look</p> <p>13 at the screen now. I just don't have --</p> <p>14 I don't know what happened with the -- I</p> <p>15 apologize.</p> <p>16 Did you rely on Langseth</p> <p>17 2008 for the basis of your opinions in</p> <p>18 this case?</p> <p>19 A. I did. It was an</p> <p>20 epidemiological study. Again, the</p> <p>21 hypothesis, mechanism of carcinogenicity</p> <p>22 may be related to inflammation. He</p> <p>23 didn't look at inflammation, but it's a</p> <p>24 hypothesis that he put forth.</p>
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<p>1 an inflammatory response in vivo."</p> <p>2 Do you agree with that?</p> <p>3 MR. FROST: Objection to</p> <p>4 form.</p> <p>5 THE WITNESS: I believe we</p> <p>6 talked about that with talc</p> <p>7 pleurodesis, yes.</p> <p>8 BY MR. SMITH:</p> <p>9 Q. -- "which may be important</p> <p>10 in ovarian cancer risk. Normal ovarian</p> <p>11 cells treated with talc are more likely</p> <p>12 to undergo cell proliferation and</p> <p>13 neoplastic transformation, and cellular</p> <p>14 generation of reactive oxygen species</p> <p>15 increases with increasing exposure to</p> <p>16 talc."</p> <p>17 Do you agree with that</p> <p>18 statement from Gates?</p> <p>19 MR. FROST: Objection to</p> <p>20 form.</p> <p>21 THE WITNESS: Gates did not</p> <p>22 show that in this publication. I</p> <p>23 do remember the statement. And I</p> <p>24 would not agree with the statement</p>	<p>1 Q. Do you believe it's a</p> <p>2 possible hypothesis?</p> <p>3 MR. FROST: Objection to</p> <p>4 form.</p> <p>5 THE WITNESS: Based upon my</p> <p>6 studies with talc, no. Because in</p> <p>7 ovarian epithelial cells and</p> <p>8 certainly in pleural -- I should</p> <p>9 say peritoneal mesothelial cells</p> <p>10 we documented antiinflammatory</p> <p>11 effects of talc. So it's</p> <p>12 difficult for me to reconcile my</p> <p>13 findings with this statement.</p> <p>14 BY MR. SMITH:</p> <p>15 Q. Collectively -- well, let me</p> <p>16 ask you this. Did you read the Mills</p> <p>17 2004 paper as reliance for your opinions</p> <p>18 in this case?</p> <p>19 A. Let me look here and see</p> <p>20 whether I did read it.</p> <p>21 No, I am uncertain what that</p> <p>22 is.</p> <p>23 I believe it might be an</p> <p>24 epidemiology study, because it does ring</p>

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<p>1 a bell.</p> <p>2 Q. You don't have it as your</p> <p>3 reliance materials for the basis of your</p> <p>4 opinion in this case; is that correct?</p> <p>5 A. No, it's not listed.</p> <p>6 Q. "Collectively, these studies</p> <p>7 point to a possible etiologic role of</p> <p>8 talc in ovarian cancer via an</p> <p>9 inflammatory process at the site of the</p> <p>10 ovarian epithelium."</p> <p>11 Would you agree or disagree</p> <p>12 with that statement from Mills?</p> <p>13 MR. FROST: Objection to</p> <p>14 form.</p> <p>15 THE WITNESS: Yeah, I would</p> <p>16 disagree that -- that has not been</p> <p>17 shown.</p> <p>18 BY MR. SMITH:</p> <p>19 Q. Have you read the Ness 2000</p> <p>20 study?</p> <p>21 A. I have. These are all</p> <p>22 hypotheses generating.</p> <p>23 I believe some of them are</p> <p>24 reviews of the field as well.</p>	<p>1 time in the literature.</p> <p>2 Q. It says, "At the same time,</p> <p>3 a growing body of epidemiological</p> <p>4 evidence suggest that factors calling</p> <p>5 epithelial inflammation are involved in</p> <p>6 ovarian carcinogenesis. Such factors</p> <p>7 include asbestos and talc exposures,</p> <p>8 endometriosis, and pelvic inflammatory</p> <p>9 disease."</p> <p>10 I take it that you don't</p> <p>11 agree with that statement of Ness in</p> <p>12 1999?</p> <p>13 MR. FROST: Objection to</p> <p>14 form.</p> <p>15 THE WITNESS: I don't. I</p> <p>16 don't agree with "such factors</p> <p>17 include." Maybe they were at the</p> <p>18 time. But there have been a lot</p> <p>19 of papers published since then</p> <p>20 that suggest the opposite.</p> <p>21 BY MR. SMITH:</p> <p>22 Q. Same study. "Inflammation</p> <p>23 by its nature produces toxic oxidants</p> <p>24 meant to kill pathogens. These oxidants</p>
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<p>1 Q. Quote, "Inflammation</p> <p>2 involves rapid cell division, DNA</p> <p>3 excision and repair, oxidative stress,</p> <p>4 and high concentrations of cytokines</p> <p>5 and" --</p> <p>6 A. Prostaglandins.</p> <p>7 Q. I'm glad you pronounced it.</p> <p>8 -- "all of which are</p> <p>9 established promoters of mutagenesis."</p> <p>10 Would you agree with that</p> <p>11 statement?</p> <p>12 MR. FROST: Objection.</p> <p>13 THE WITNESS: In a general</p> <p>14 context, yes. But it certainly</p> <p>15 hasn't been shown for talc,</p> <p>16 because talc doesn't induce</p> <p>17 mutations.</p> <p>18 BY MR. SMITH:</p> <p>19 Q. Have you relied on Ness 1999</p> <p>20 in forming the basis of your opinions in</p> <p>21 this case?</p> <p>22 A. Yes. It's somewhat</p> <p>23 outdated, but I think that this was a</p> <p>24 review of the state of the art at that</p>	<p>1 cause direct damage to DNA, proteins, and</p> <p>2 lipids and may, therefore, play a role in</p> <p>3 direct carcinogenesis."</p> <p>4 Do you agree with that</p> <p>5 statement?</p> <p>6 MR. FROST: Objection.</p> <p>7 THE WITNESS: Again, it's a</p> <p>8 general statement with regard to</p> <p>9 inflammation in general. I don't</p> <p>10 agree with it as it's been</p> <p>11 shown -- has not been shown to be</p> <p>12 important in ovarian cancer</p> <p>13 development.</p> <p>14 BY MR. SMITH:</p> <p>15 Q. Same study. "Direct</p> <p>16 induction of inflammation as a result of</p> <p>17 endometriosis, talc and asbestos exposure</p> <p>18 and PID, as well as ovulation itself, may</p> <p>19 act to promote ovarian tumorigenesis."</p> <p>20 Do you agree with that</p> <p>21 statement from Ness?</p> <p>22 MR. FROST: Objection.</p> <p>23 THE WITNESS: Again, it's an</p> <p>24 outdated paper that hasn't</p>

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<p>1 evaluated these studies that don't</p> <p>2 support that mechanism of action.</p> <p>3 BY MR. SMITH:</p> <p>4 Q. Same study. "We have</p> <p>5 reviewed the data suggesting that an</p> <p>6 additional mechanism that may underlie</p> <p>7 ovarian cancer is inflammation with</p> <p>8 concomitant rapid DNA turnover and</p> <p>9 defective repair."</p> <p>10 Do you agree or disagree</p> <p>11 with that statement?</p> <p>12 MR. FROST: Objection.</p> <p>13 THE WITNESS: Again, I -- it</p> <p>14 may have been true in 1999, but</p> <p>15 data do not support that as a</p> <p>16 whole.</p> <p>17 BY MR. SMITH:</p> <p>18 Q. Okay. Well, let's talk</p> <p>19 about data that might be more relevant.</p> <p>20 And you would agree that this is</p> <p>21 epidemiological data that we have gone</p> <p>22 through regarding the inflammation that's</p> <p>23 on Exhibit 24, correct?</p> <p>24 MR. FROST: Objection.</p>	<p>1 stapled.</p> <p>2 (Document marked for</p> <p>3 identification as Exhibit</p> <p>4 Mossman-25.)</p> <p>5 BY MR. SMITH:</p> <p>6 Q. All right. Exhibit 25, this</p> <p>7 is a paper that was published in 2009.</p> <p>8 Do you see that, Doctor? "Inflammation:</p> <p>9 A Hidden Path to Breaking the Spell of</p> <p>10 Ovarian Cancer."</p> <p>11 Do you see that?</p> <p>12 A. Yes. I am not familiar with</p> <p>13 the journal Cell Cycle, but...</p> <p>14 Q. By Shan and Liu.</p> <p>15 And if you turn to the next</p> <p>16 page -- well, let me ask you this. Is</p> <p>17 this on your reference materials that</p> <p>18 form the basis of your opinion in this</p> <p>19 case?</p> <p>20 A. No. And I'm unfamiliar with</p> <p>21 the journal. So I'm not sure it would</p> <p>22 have been referenced by PubMed or my</p> <p>23 PubMed searches.</p> <p>24 Q. Okay. Well, let's go to the</p>
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<p>1 THE WITNESS: I would agree,</p> <p>2 I'm sorry. Was that a question?</p> <p>3 BY MR. SMITH:</p> <p>4 Q. Been dealing with</p> <p>5 epidemiological studies?</p> <p>6 A. Have we talked about them?</p> <p>7 Q. Yes.</p> <p>8 A. Yes, we have.</p> <p>9 Q. Excuse me. That are</p> <p>10 included in Exhibit 24 that we went</p> <p>11 through all the quotes. Those are</p> <p>12 epidemiological studies that we went</p> <p>13 through, correct?</p> <p>14 MR. FROST: Objection.</p> <p>15 THE WITNESS: The majority</p> <p>16 of these are epidemiology studies,</p> <p>17 yes, with the exception of the</p> <p>18 Trabert study.</p> <p>19 MR. FROST: Are these two</p> <p>20 different ones?</p> <p>21 MR. SMITH: No.</p> <p>22 MR. FROST: Okay.</p> <p>23 MR. SMITH: Same one.</p> <p>24 MR. FROST: Just not</p>	<p>1 first page. "Inflammation: A hidden</p> <p>2 path to breaking the spell of ovarian</p> <p>3 cancer." Shan and Liu, the authors from</p> <p>4 the department of pathology at the</p> <p>5 University of Texas M.D. Anderson Cancer</p> <p>6 Center, Houston, Texas.</p> <p>7 Is M.D. Anderson Cancer</p> <p>8 Center in Houston, Texas, a reputable</p> <p>9 cancer center in the United States and</p> <p>10 throughout the world?</p> <p>11 MR. FROST: Objection.</p> <p>12 THE WITNESS: It is.</p> <p>13 BY MR. SMITH:</p> <p>14 Q. Let's go to the first --</p> <p>15 let's go to the box, grey box to the left</p> <p>16 above introduction. "Epithelial ovarian</p> <p>17 cancer is a highly lethal gynecological</p> <p>18 cancer for which overall prognosis has</p> <p>19 remained poor over the past few decades.</p> <p>20 A number of theories have been postulated</p> <p>21 in an effort to explain the etiology of</p> <p>22 epithelial ovarian cancer each of which</p> <p>23 has been both applauded and doubted. Of</p> <p>24 note, these theories likely are not</p>

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<p style="text-align: right;">Page 266</p> <p>1 mutually exclusive as they all converge 2 more or less on the role of inflammation 3 in promoting ovarian tumorigenesis." 4 Do you agree with that 5 statement? 6 MR. FROST: Objection. 7 THE WITNESS: Yes. That the 8 inflammation certainly has been 9 shown to be important in late 10 stage cancers, including ovarian. 11 BY MR. SMITH: 12 Q. That's not what it says, 13 Doctor. It says, "Of note, these 14 theories are likely not mutually 15 exclusive as they all converge more or 16 less on the role of inflammation in 17 promoting ovarian tumorigenesis," 18 correct? 19 A. Correct. 20 Q. Okay. 21 A. And promotion is not 22 initiation or causation. 23 Q. I understand. 24 A. So that's what I stated.</p>	<p style="text-align: right;">Page 268</p> <p>1 Q. Sure. 2 A. -- uncover where -- 3 Q. We're going to go through 4 it. We're going to go through it. 5 A. Okay. 6 Q. All right. 7 Introduction. "Epithelial 8 ovarian cancer, EOC, is the most common 9 subgroup of ovarian cancer. It's the 10 deadliest gynecological cancer in the 11 United States, accounting for more deaths 12 than all other gynecological cancers 13 combined." 14 And we went through that 15 earlier, correct? 16 A. Yes. 17 Q. "The high mortality rate for 18 epithelial ovarian cancer is a result of 19 technical obstacles to early detection of 20 the disease, a high prevalence of distal 21 metastasis at late stages of the 22 disease" -- and that's in 70 percent of 23 the cases it said. 24 "This latter property is</p>
<p style="text-align: right;">Page 267</p> <p>1 That in general, 2 inflammation has been linked to the 3 progression as well as the dissemination 4 of preexisting tumors. 5 Q. Okay. Let me continue. "In 6 this review we describe the latest 7 studies on the role of inflammation in 8 the initiation and progression of 9 epithelial ovarian cancer from three 10 major aspects: Physiologic functions of 11 a normal ovary, potential involvement of 12 the fallopian tube in the initiation of 13 epithelial ovarian cancer, and the strong 14 impact of cellular microenvironment on 15 the development of disease." 16 Now, that statement doesn't 17 just say progression. It says 18 initiation, correct? 19 MR. FROST: Objection. 20 THE WITNESS: We describe 21 the latest studies on the role of 22 inflammation initiation. I'd 23 like -- I'd have to read this -- 24 BY MR. SMITH:</p>	<p style="text-align: right;">Page 269</p> <p>1 probably attributable to the unique 2 peritoneal environment of the epithelial 3 ovarian cancer which facilitates 4 convenient seating of ovarian cancer 5 cells in the peritoneal cavity, which is 6 further aided by the constant flow of 7 peritoneal fluid." 8 Were you aware of that 9 statement prior to us reading it? 10 A. Could you refer -- you're 11 going a little fast. I'm just wondering 12 where you are. 13 Q. I'm at introduction. 14 A. Okay. 15 Q. And I'm about six lines 16 down, "This latter property is probably 17 attributable." 18 Do you see that? 19 A. The first paragraph? 20 Q. Under introduction. 21 A. Yep. 22 Q. It's after "70 percent of 23 the cases." 24 Are you aware of the unique</p>

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<p>1 environment of peritoneal -- the 2 peritoneal environment being unique for 3 epithelial ovarian cancer which 4 facilitates convenient seating of ovarian 5 cancer cells in the peritoneal cavity, 6 which is further aided by constant flow 7 of peritoneal fluid." 8 Were you aware of that 9 statement prior to us reading that now? 10 MR. FROST: Objection to 11 form. 12 THE WITNESS: Yeah. I'm 13 still lost in where you are here, 14 and whether there are references 15 to that statement. 16 BY MR. SMITH: 17 Q. Ma'am. Ma'am. I'm in 18 introduction. 19 A. Gotcha. 20 Q. On the first page. 21 A. Okay. 22 Q. Do you see, one, two, three, 23 four, five, six, seven lines down, you 24 see 70 percent of cases right there?</p>	<p>1 trends. 2 So I think the word unique 3 peritoneal environment is of 4 question to me. I don't know why 5 it would be unique. 6 BY MR. SMITH: 7 Q. Okay. "We call particular 8 attention to this 'open' environment to 9 which epithelial ovarian cancer is 10 exposed because it has resulted in a 11 myriad of characteristics specific to 12 epithelial ovarian cancer such as ease of 13 widespread cancer metastases" -- 14 "metastases in short period of time, 15 unique formation of ascites, and high 16 susceptibility of the ovarian surface 17 epithelium or OSE to peritoneal 18 inflammatory stimuli." 19 A. Again, I think by open 20 environment they are talking about the 21 peritoneum as a cavity with fluids in it. 22 I don't recall nor have I seen papers 23 suggesting that there is high 24 susceptibility of ovarian epithelial to</p>
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<p>1 Do you see 70 percent? 2 A. Yes. 3 Q. I'm reading the line right 4 after that. "This latter property is 5 probably attributable to the unique 6 peritoneal environment of epithelial 7 ovarian cancer which facilitates 8 convenient seating of ovarian cancer 9 cells in the peritoneal cavity, which is 10 further aided by the constant flow of 11 peritoneal fluid." 12 Were you aware of that fact 13 before we read it just now? 14 MR. FROST: Objection. 15 THE WITNESS: I was aware of 16 the importance of tumor 17 microenvironment on dissemination 18 of preexisting cancers. I'm not 19 sure whether -- how unique a 20 peritoneal environment is. Since 21 we have looked at the environment 22 of the peritoneum and the lung in 23 terms of cytokines in regard to 24 mesotheliomas and see very similar</p>	<p>1 peritoneal inflammatory stimuli. 2 Again, this is a -- not -- 3 not a paper with original results. It's 4 a hypothesis paper. I don't see any data 5 here supporting that, or any data at all 6 in this manuscript other than a figure 7 entitled, "Potential sources of 8 inflammatory stimuli." 9 Q. Go to the next page, please. 10 A. Mm-hmm. 11 Q. If you look down at the 12 bottom right. "Inflammation: Cellular 13 senescence in ovarian epithelial 14 microenvironment and ovarian cancer." 15 "As described above the 16 complex biology of OSE," which is ovarian 17 surface epithelium, "makes ovarian 18 epithelial cells exceedingly sensitive to 19 peritoneal inflammatory agents." 20 And they talk about the open 21 system on the page we read just before 22 that. Do you recall that? 23 A. Yeah, but again I want to 24 emphasize that they are talking about</p>

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<p style="text-align: right;">Page 274</p> <p>1 Figure 1, "Potential sources of 2 inflammatory stimuli." And there's no 3 data to support this hypothesis in the 4 paper. 5 Q. It doesn't say hypothesis 6 anywhere, does it, Doctor? 7 MR. FROST: Objection. 8 THE WITNESS: This is a 9 hypothesis paper. There's no data 10 in it. This is a figure that they 11 have drawn, a schematic in which 12 they are hypothesizing that there 13 is inflammatory stimuli in the 14 peritoneal fluids. 15 So I'm unclear as to the 16 data. I think it's an intriguing 17 hypothesis. But as I emphasized 18 previously, it hasn't been borne 19 out in the last decade. 20 BY MR. SMITH: 21 Q. Okay. Let's look at Figure 22 1. It has -- at the bottom right. It 23 has, "Peritoneal inflammatory stimuli, 24 initiation of premalignant ovarian</p>	<p style="text-align: right;">Page 276</p> <p>1 been described as one enriched with a 2 broad spectrum pro-inflammatory cytokines 3 and chemokines. Increasing evidence 4 suggests that inflammation contributes 5 significantly to the etiology of 6 epithelial ovarian cancer." 7 What does "etiology" mean? 8 A. Basically the process of 9 disease. 10 Again, there's no references 11 to support this. So I'm not sure what he 12 means by etiology. It's a very broad 13 term. 14 Q. Okay. Let's go to -- hold 15 on a second. Bear with me just a second. 16 Man, they did a weird way of 17 copying this stuff down there. I mean, 18 you talking about -- I couldn't figure it 19 out. It all just came to me. And I just 20 can't believe what I'm seeing. But 21 anyway, we'll get it straight. 22 MR. FROST: Is this one 23 copy? 24 MR. SMITH: Yeah, I'm</p>
<p style="text-align: right;">Page 275</p> <p>1 epithelial cells, senescent fibroblasts, 2 inflammatory cells, and capillaries." 3 Do you see that diagram in 4 Figure C? 5 A. Yes. 6 Q. And it says under Figure 1, 7 "Potential sources of inflammatory 8 stimuli that may contribute to the 9 initiation and/or progression of 10 epithelial ovarian cancer." 11 Do you see that? 12 A. I do. And it also states 13 that these functions may be 14 pro-inflammatory in nature. 15 So, again, this is an 16 intriguing hypothesis, but it was in 17 2009. And in ten years there's no 18 evidence suggesting that this hypothesis 19 is true. 20 Q. We'll get to that. Let's go 21 to the page, the last page conclusions. 22 A. Okay. 23 Q. "The tumor milieu in which 24 epithelial ovarian cancer develops has</p>	<p style="text-align: right;">Page 277</p> <p>1 getting ready to hand it to you 2 now. 3 (Document marked for 4 identification as Exhibit 5 Mossman-26.) 6 (Whereupon, a discussion was 7 held off the record.) 8 BY MR. SMITH: 9 Q. Okay. Doctor, this is a 10 study not from back in time. This is 11 August 2018, a year ago, correct? 12 A. Yes. It's in another 13 journal that I have never heard of. So 14 I'm just trying to see whether it would 15 have appeared on my PubMed searches. 16 Q. Down at the bottom left, it 17 has NCBI, which is the public release of 18 government -- and it has NIH.gov. What 19 is NIH? 20 A. That means it's referenced 21 in the National Institutes or National 22 Library of Medicine. 23 Q. It's the National Institute 24 of Health, correct?</p>

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<p>1 A. NIH is the National 2 Institutes of Health. I don't think the 3 study was done at the National Institutes 4 of Health. 5 Q. And this study is entitled 6 The Role of Inflammation and Inflammatory 7 Mediators in the Development, 8 Progression, Metastasis and 9 Chemoresistance of Epithelial Ovarian 10 Cancer, correct? 11 A. Yes. This appears to be 12 another review with no new data. Allow 13 me to just go through this. 14 Q. I'm going to read some 15 sections in the abstract. "Inflammation 16 plays a role in the initiation and 17 development of many types of cancers, 18 including epithelial ovarian cancer (EOC) 19 and high-grade serous ovarian cancer 20 (HGSC), a type of epithelial ovarian 21 cancer." 22 Do you agree or disagree 23 with that statement in the abstract of 24 this paper?</p>	<p>1 A. Prostaglandins. 2 Q. Thank you. 3 -- "prostaglandins, and 4 growth factors that contribute to 5 increase cell division and genetic and 6 epigenetic changes." 7 Do you agree with those 8 statements? 9 MR. FROST: Objection to 10 form. 11 THE WITNESS: I believe that 12 this is a generalized statement in 13 terms of epithelial cells, but not 14 with regard to ovarian epithelial 15 cells. 16 BY MR. SMITH: 17 Q. "These exposure-induced 18 changes promote" -- we just went through 19 that. "Furthermore, the pro-inflammatory 20 tumor microenvironment (TME) contributes 21 to epithelial ovarian cancer and 22 metastases" -- 23 A. Metastases. 24 Q. I don't know why I'm</p>
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<p>1 A. I disagree. This is a 2 review. And I don't believe that 3 inflammation has been linked to the 4 initiation of epithelial ovarian cancers 5 or serous grades. 6 Q. Okay. 7 A. So I would -- I think it's 8 an emphatic statement that needs to be 9 referenced. 10 Q. There are -- this is the 11 abstract. "There are connections" -- and 12 we'll get to it. 13 A. Okay. 14 Q. "There are connections 15 between epithelial ovarian cancer in both 16 peritoneal and ovulation-induced 17 inflammation. Additionally, epithelial 18 ovarian cancers have an inflammatory 19 component that contributes to their 20 progression. At sites of inflammation, 21 epithelial cells are exposed to increased 22 levels of inflammatory mediators, such as 23 reactive oxygen species, cytokines" -- 24 pronounce that for me, please.</p>	<p>1 tripping over my words today. 2 -- "and chemo resistance. 3 In this review, we will discuss the roles 4 inflammation and inflammatory mediators 5 play in the development, progression, 6 metastases and chemoresistance of 7 epithelial ovarian cancer." 8 Correct? 9 MR. FROST: Objection to 10 form. 11 THE WITNESS: Yes, this is a 12 review that discusses that. 13 BY MR. SMITH: 14 Q. Okay. And the first 15 paragraph is, "Inflammation and 16 epithelial ovarian cancer." 17 Do you see that? 18 A. I do. 19 Q. And it states, "Inflammation 20 is part of the immune response that 21 protects against foreign pathogens and 22 aids in healing. Inflammation is 23 elicited in response to cellular damage 24 by infection, exposure to foreign</p>

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<p style="text-align: right;">Page 282</p> <p>1 particles or pollutants or irritants, or  2 an increase in cellular stress. The  3 ultimate goal of the inflammatory  4 response is to restore tissue  5 homeostasis, either by destruction or  6 healing of the damaged tissue.  7 "The acute or immediate  8 inflammatory response involves  9 modification of the vasculature  10 surrounding the site of stress or damage  11 to increase blood flow. This alteration  12 is then followed by activation of innate  13 immune cells already present in the  14 tissue including macrophages, dendritic  15 cells (DC) and mast cells and an increase  16 in infiltration of additional innate  17 immune cells into the affected tissue."  18 Do you agree with that?  19 MR. FROST: Objection.  20 THE WITNESS: It's a  21 generalized statement for  22 inflammation, yes.  23 BY MR. SMITH:  24 Q. It says, "At sites of</p>	<p style="text-align: right;">Page 284</p> <p>1 A. I do.  2 Q. The next paragraph talks  3 about ovarian cancer. And it states --  4 one, two, three -- four lines down,  5 "Chronic inflammation is an important  6 risk factor associated with epithelial  7 ovarian cancer and high-grade serous  8 ovarian cancer (HGSC), the most malignant  9 subtype of epithelial ovarian cancer."  10 Do you agree with that?  11 A. I don't see a statement for  12 that. I know inflammation has been  13 associated with late stage tumors, but we  14 don't know what the role is in terms of  15 disease or protection from disease and  16 what is the function of this.  17 Q. "In this review, we will be  18 primarily focus on inflammation as a risk  19 factor for invasive epithelial ovarian  20 cancer, but have also included supportive  21 evidence from other ovarian cancer  22 subtypes studied that do not describe the  23 subtype of ovarian cancer and other tumor  24 types as indicated."</p>
<p style="text-align: right;">Page 283</p> <p>1 inflammation, there are high levels of  2 reactive oxygen species, cytokines,  3 chemokines, and growth factors that are  4 produced by the immune cells and other  5 cells in tissue."  6 Do you agree with that?  7 MR. FROST: Objection to  8 form.  9 THE WITNESS: I agree that  10 this may be true in chronic  11 inflammation or extremely high  12 exposures to very toxic agents.  13 So in that vein, I would agree  14 with it.  15 BY MR. SMITH:  16 Q. "Acute inflammation is  17 essential for the tissue homeostasis and  18 to protect against normal exposure to  19 pathogens. However, in certain cases,  20 the body is unable to resolve this  21 response or is subjected to repeated  22 stimulation, resulting in chronic  23 inflammation."  24 Do you agree with that?</p>	<p style="text-align: right;">Page 285</p> <p>1 And then they go through and  2 they talk about, on the next page --  3 well, they talk about signaling pathways  4 and transcription factors and innate  5 immune response. It talks about the  6 immune responses.  7 Number 2 on the next page  8 talks about inflammation as a risk factor  9 for epithelial ovarian cancer. It has  10 cites there. It talks about ovulation.  11 It talks about infection.  12 And then it says, "Other  13 sources of inflammation."  14 Do you see that on Page 4 of  15 39?  16 A. I do.  17 Q. And it says, "The other  18 causes of inflammation in the ovaries  19 and/or fallopian tubes are endometriosis,  20 obesity, polycystic ovarian syndrome or  21 PCOS, and talc exposure."  22 Do you agree with that?  23 MR. FROST: Objection to  24 this and the prior question which</p>

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<p>1 sort of bleed together.</p> <p>2 THE WITNESS: Yeah, again</p> <p>3 there's no reference for -- for</p> <p>4 this statement. So I -- I</p> <p>5 disagree with it. Because talc</p> <p>6 exposures have not been linked to</p> <p>7 inflammation in the ovaries. And</p> <p>8 I think I've covered all the</p> <p>9 information that I reviewed to</p> <p>10 reach that conclusion. So this is</p> <p>11 a review by cell biologists in a</p> <p>12 low-impact journal I've never</p> <p>13 heard from or seen before.</p> <p>14 But in looking at the</p> <p>15 original data which is not</p> <p>16 relevant --</p> <p>17 BY MR. SMITH:</p> <p>18 Q. Whoa, whoa. Hold on a</p> <p>19 second. Low-impact journal. What do you</p> <p>20 base that on?</p> <p>21 A. I've never heard of Cancers.</p> <p>22 I've heard --</p> <p>23 Q. Listen -- how do you know</p> <p>24 what the -- tell me what the impact</p>	<p>1 the next page, Page 5 of 39. And you go</p> <p>2 three paragraphs down. It says, "Talc is</p> <p>3 a silicate mineral and exposure to it can</p> <p>4 cause inflammation of the ovaries and</p> <p>5 poses a risk hazard for the development</p> <p>6 of epithelial ovarian cancer."</p> <p>7 Do you agree with that</p> <p>8 statement or not?</p> <p>9 A. Let me look up Reference 45</p> <p>10 and I'll tell you.</p> <p>11 No.</p> <p>12 Q. "It has been proposed that</p> <p>13 talc from talcum powder used for dusting</p> <p>14 and from condoms in the vaginal</p> <p>15 diaphragms can migrate up the fallopian</p> <p>16 tubes in retrograde flow of fluids and</p> <p>17 mucus and get lodged in the ovaries.</p> <p>18 Tubal ligation, which is protective for</p> <p>19 epithelial ovarian cancer is thought to</p> <p>20 block the transport of talc from lower</p> <p>21 genital -- from the lower genital tract.</p> <p>22 Talc behaves as a foreign particle,</p> <p>23 triggering an inflammatory response and</p> <p>24 has two sites. The talc attracts</p>
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<p>1 factor is then, for this journal.</p> <p>2 A. If I haven't seen it, let me</p> <p>3 guess --</p> <p>4 Q. No, ma'am, I don't want a</p> <p>5 guess --</p> <p>6 A. -- it's going to be lower --</p> <p>7 Q. -- I want you to tell me</p> <p>8 what the impact factor for this journal</p> <p>9 is.</p> <p>10 A. We can look it up. Why</p> <p>11 don't we look it up?</p> <p>12 Q. No, ma'am. You said it was</p> <p>13 a low-impact journal and you said --</p> <p>14 A. I have never heard of it --</p> <p>15 Q. I understand.</p> <p>16 A. -- so, yes.</p> <p>17 Q. I understand. I want you to</p> <p>18 tell me what your basis -- your basis for</p> <p>19 that is because you've never heard of it.</p> <p>20 A. I have -- I am aware of all</p> <p>21 the cancer journals that are high profile</p> <p>22 and high impact. This is not one of</p> <p>23 them.</p> <p>24 Q. Okay. We'll go to page --</p>	<p>1 macrophages, which then try to</p> <p>2 phagocytose it. The macrophages then</p> <p>3 send chemotactic signals to other immune</p> <p>4 response mediators and initiate a wound</p> <p>5 healing. Since talc is not degraded by</p> <p>6 the body, it inhibits the wound healing</p> <p>7 process, resulting in chronic</p> <p>8 inflammation."</p> <p>9 Would you agree with those</p> <p>10 statements?</p> <p>11 MR. FROST: Objection.</p> <p>12 THE WITNESS: No, and they</p> <p>13 are not supported by the</p> <p>14 references. We can go through</p> <p>15 these. But these statements</p> <p>16 aren't supported by the</p> <p>17 references.</p> <p>18 In fact, 47 is a paper by</p> <p>19 Muscat and Huncharek on perineal</p> <p>20 talc use and ovarian cancer, a</p> <p>21 critical review. It concludes</p> <p>22 that talc is not associated with</p> <p>23 ovarian cancer risk.</p> <p>24 BY MR. SMITH:</p>



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<p>1 Q. No, no, no.</p> <p>2 A. So --</p> <p>3 Q. Doctor, it says, "Talc,</p> <p>4 there is not a case for causality."</p> <p>5 A. Right.</p> <p>6 Q. The -- the study published a</p> <p>7 statistically significant increased risk</p> <p>8 of ovarian cancer from genital talc use.</p> <p>9 MR. FROST: Objection.</p> <p>10 THE WITNESS: No.</p> <p>11 BY MR. SMITH:</p> <p>12 Q. It does not?</p> <p>13 A. Muscat and Huncharek do not</p> <p>14 make --</p> <p>15 Q. Paid experts from the</p> <p>16 defendants.</p> <p>17 A. Pardon me?</p> <p>18 MR. FROST: Objection.</p> <p>19 BY MR. SMITH:</p> <p>20 Q. Did you know that they were</p> <p>21 paid experts from the defendants when</p> <p>22 they wrote this paper?</p> <p>23 A. No --</p> <p>24 Q. Okay.</p>	<p>1 inconsistent statements that are not</p> <p>2 supported by the references they cite.</p> <p>3 Q. Doctor, did you use</p> <p>4 Huncharek and Muscat as a basis for your</p> <p>5 opinions in this case, this reference</p> <p>6 here?</p> <p>7 A. It was one of several</p> <p>8 reviews, yes.</p> <p>9 Q. And you are stating that</p> <p>10 that paper did not reveal a statistically</p> <p>11 significant increased risk of ovarian</p> <p>12 cancer from genital talc use?</p> <p>13 MR. FROST: Objection to</p> <p>14 form.</p> <p>15 THE WITNESS: I would go</p> <p>16 back to that paper and see how it</p> <p>17 was worded, but the conclusions of</p> <p>18 the authors were that talc did not</p> <p>19 play a role in the causation of</p> <p>20 ovarian cancers.</p> <p>21 BY MR. SMITH:</p> <p>22 Q. Did the epidemiological</p> <p>23 study that is referenced here of Muscat</p> <p>24 and Huncharek conclude that there was a</p>
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<p>1 A. -- this was in 2008. And</p> <p>2 they concluded that there was not an</p> <p>3 association. Yet this individual is</p> <p>4 citing this reference to support the</p> <p>5 statement "talc behaves as a foreign</p> <p>6 particle triggering an inflammatory</p> <p>7 response." And it's wrong. The paper is</p> <p>8 wrong, and the references that it uses</p> <p>9 are wrong.</p> <p>10 Heller didn't show that.</p> <p>11 Henderson didn't show that. Henderson is</p> <p>12 an editorial.</p> <p>13 So I would really question</p> <p>14 the source of this supposed journal</p> <p>15 called Cancers that I've never heard of,</p> <p>16 while -- and we have --</p> <p>17 Q. Let me ask -- I'm sorry, I</p> <p>18 didn't mean to cut you off.</p> <p>19 A. Yeah.</p> <p>20 Q. Go ahead.</p> <p>21 A. But -- we can still spend</p> <p>22 time going through it, but it's not going</p> <p>23 to alter my opinion that these authors</p> <p>24 wrote a very sloppy paper with</p>	<p>1 statistically significant increased risk</p> <p>2 of ovarian cancer from genital talc use?</p> <p>3 A. I --</p> <p>4 MR. FROST: Objection to</p> <p>5 form.</p> <p>6 THE WITNESS: Yeah. I'd</p> <p>7 have to go back and look at the</p> <p>8 paper --</p> <p>9 BY MR. SMITH:</p> <p>10 Q. Okay.</p> <p>11 A. -- to see whether that was</p> <p>12 stated as such.</p> <p>13 Q. Now, under NSAIDS and</p> <p>14 reduced risk of epithelial ovarian</p> <p>15 cancer.</p> <p>16 "Further connecting</p> <p>17 inflammation to the epithelial ovarian</p> <p>18 cancer are several studies that</p> <p>19 demonstrate the intake of nonsteroidal</p> <p>20 antiinflammatory drugs, or NSAIDs,</p> <p>21 specifically of aspirin, correlates</p> <p>22 adversely with the risk of epithelial" --</p> <p>23 A. Are we going back to this</p> <p>24 review in Cancers?</p>

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<p>1 Q. Yes.</p> <p>2 A. Or for --</p> <p>3 MR. FROST: Yeah, I was</p> <p>4 going to say, what page are you</p> <p>5 on?</p> <p>6 THE WITNESS: Yeah.</p> <p>7 MR. SMITH: I'm on Page 5.</p> <p>8 Excuse me. I'm right below where</p> <p>9 I was reading.</p> <p>10 MR. FROST: Oh, I see.</p> <p>11 Section 2.4?</p> <p>12 MR. SMITH: Yep.</p> <p>13 BY MR. SMITH:</p> <p>14 Q. "Further connecting</p> <p>15 inflammation to epithelial ovarian cancer</p> <p>16 are several studies that demonstrate that</p> <p>17 intake of nonsteroidal antiinflammatory</p> <p>18 drugs, NSAIDs, specifically of aspirin,</p> <p>19 correlates inversely with risk of ovarian</p> <p>20 cancer and endometrial cancer," and it</p> <p>21 has cites there.</p> <p>22 Do you see that, Doctor?</p> <p>23 A. I do, and again these</p> <p>24 studies are controversial and the</p>	<p>1 point it to her?</p> <p>2 MR. SMITH: That's fine.</p> <p>3 THE WITNESS: Yeah. Okay.</p> <p>4 BY MR. SMITH:</p> <p>5 Q. "Oxidative stress has also</p> <p>6 been shown to facilitate epigenetic</p> <p>7 mechanisms in many cancers including</p> <p>8 epithelial ovarian cancer."</p> <p>9 Would you agree or disagree</p> <p>10 with that statement?</p> <p>11 A. Let me look at Reference 86</p> <p>12 and see whether it makes sense.</p> <p>13 No that's not supported by</p> <p>14 that.</p> <p>15 Q. Okay.</p> <p>16 A. It's another misquote. It's</p> <p>17 talking about tumor suppressor genes in</p> <p>18 ovarian cancer.</p> <p>19 Q. You've never seen this</p> <p>20 document, and you haven't seen the</p> <p>21 document reference. So you don't know</p> <p>22 what it says, do you, Doctor?</p> <p>23 MR. FROST: Objection.</p> <p>24 THE WITNESS: I can read the</p>
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<p>1 statement that he puts forth does not</p> <p>2 agree with a lot of the studies.</p> <p>3 And let me check which ones</p> <p>4 he's referencing, but I wouldn't agree</p> <p>5 with this statement.</p> <p>6 Q. Okay. Go to Page 11 of 39,</p> <p>7 if you look at the bottom. It's 3.1.</p> <p>8 It's ROS and oxidative stress.</p> <p>9 Do you see it?</p> <p>10 A. I do.</p> <p>11 Q. And if you go to the -- one,</p> <p>12 two, three -- fourth paragraph. The</p> <p>13 paragraph at the bottom says, "Oxidative</p> <p>14 stress has also been shown to facilitate</p> <p>15 epigenetic mechanisms in many cancers,</p> <p>16 including epithelial ovarian cancer."</p> <p>17 Would you agree or disagree</p> <p>18 with that?</p> <p>19 MR. FROST: Objection.</p> <p>20 THE WITNESS: Let's go -- so</p> <p>21 we're on the third paragraph and</p> <p>22 what sentence are you talking</p> <p>23 about?</p> <p>24 MR. FROST: Do you mind if I</p>	<p>1 title.</p> <p>2 BY MR. SMITH:</p> <p>3 Q. Well, that's not the whole</p> <p>4 paper though, is it, Doctor?</p> <p>5 A. Epigenetic mechanisms.</p> <p>6 Okay. We're talking about tumor</p> <p>7 suppressor genes and methylation. It's</p> <p>8 an epigenetic mechanism. OS, I have no</p> <p>9 idea what that means.</p> <p>10 Q. Do you agree or disagree</p> <p>11 with the statement, "Oxidative stress has</p> <p>12 also been shown to facilitate epigenetic</p> <p>13 mechanisms in many cancers including</p> <p>14 epithelial ovarian cancer"?</p> <p>15 A. It looks like, to me, that</p> <p>16 this Reference 86 is talking about</p> <p>17 methylation of tumor suppression genes</p> <p>18 and is not exploring the oxidative stress</p> <p>19 by any agents on these genes.</p> <p>20 Q. Do you agree or disagree</p> <p>21 with the statement?</p> <p>22 MR. FROST: Objection.</p> <p>23 THE WITNESS: I agree with</p> <p>24 oxidative stress has been shown to</p>

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<p style="text-align: right;">Page 298</p> <p>1 facilitate epigenetic mechanisms. 2 Again, I question whether 3 Reference 86 used oxidative stress 4 insults to look at methylation of 5 tumor suppressor genes. And I 6 doubt that they did from the 7 title. 8 BY MR. SMITH: 9 Q. You doubt they did. You 10 don't know, correct? 11 MR. FROST: Objection. 12 THE WITNESS: No. Unless 13 you have the paper. I'd be 14 delighted to look at it. 15 BY MR. SMITH: 16 Q. And the statement talks 17 about, "Oxidative stress has also been 18 shown to facilitate epigenetic mechanisms 19 in many cancers, including epithelial 20 ovarian cancer." 21 Would you agree with that? 22 MR. FROST: Objection. 23 THE WITNESS: No. I just 24 said that I don't agree with it,</p>	<p style="text-align: right;">Page 300</p> <p>1 A. I do. 2 Q. This is on Oncotarget. Are 3 you familiar with Oncotarget? 4 A. Yes, I reviewed for them. 5 Q. "Oxidative Stress in Female 6 Cancers." And you're a reviewer of this 7 publication, right? 8 A. I didn't review this 9 publication, no. 10 Q. You said that you were a 11 reviewer of this Oncotarget, correct? 12 A. Oncotarget is a journal, and 13 I review papers for Oncotarget 14 occasionally. I have not seen this 15 paper. 16 Q. Okay. And it states, 17 "Abstract: Breast, cervical, and ovarian 18 cancer are highly prevalent in women 19 worldwide. Environmental, hormonal, and 20 viral-related factors are especially 21 relevant in the development of these 22 tumors. These factors are strongly 23 related to oxidative stress through the 24 generation of reactive oxygen species."</p>
<p style="text-align: right;">Page 299</p> <p>1 because I don't believe that that 2 statement is reflected in the 3 title of Number 86. So I'd have 4 to see the paper. 5 But based upon the 6 references that you've pointed me 7 to already, I am suspicious 8 whether it does or not. 9 MR. SMITH: Okay. Let's 10 see. I don't think I marked that 11 as an exhibit, did I? 12 MR. FROST: No. 13 MR. SMITH: I did something 14 with my exhibit stickers. 15 That's 26. 16 (Document marked for 17 identification as Exhibit 18 Mossman-27.) 19 BY MR. SMITH: 20 Q. I want to next -- this is 21 another 2018 article, and it has the NCBI 22 NN -- NLM, NIH.gov reference at the 23 bottom. 24 Do you see that, Doctor?</p>	<p style="text-align: right;">Page 301</p> <p>1 Would you agree with that? 2 MR. FROST: Objection. 3 THE WITNESS: These 4 factors -- okay. Environmental, 5 hormonal, and viral-related 6 factors. I don't know what 7 they're talking about here. But 8 they're -- 9 BY MR. SMITH: 10 Q. Okay. Well, we'll read the 11 whole abstract. 12 A. Okay. 13 Q. "The oxidative stress is 14 caused by an imbalance in the redox 15 status of the organism and is literally 16 defined as 'an imbalance between ROS 17 generation and its detoxification by 18 biological system, leading to the 19 impairment of damage repair by 20 cells/tissue.' 21 "The multi-step progression 22 of cancer suggests that oxidative stress 23 is involved in cancer initiation, 24 promotion, and progression. In this</p>

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<p>1 review, we describe role of oxidative 2 stress and the interplay with 3 environmental, host, and viral factors 4 related to breast, cervical, and ovarian 5 cancers, initiation, promotion and 6 progression. 7 "In addition, the role of 8 natural antioxidant compounds, human and 9 other, compounds for breast, cervical, 10 and ovarian cancers' prevention/treatment 11 is discussed." 12 Do you see that? 13 A. Yes. This is a review. 14 Q. Do you agree with that 15 abstract? 16 A. As what they're describing, 17 I'd have to assume that's what they're 18 describing and see the references that 19 support their statements. 20 Q. Go to the conclusions. It's 21 on Page 16 of 30, Doctor. 22 "Conclusions and remarks." 23 And if you go down five lines, and you go 24 all the way to the right, it says, "We</p>	<p>1 Do you agree with that 2 statement? 3 A. I do. And as I emphasized 4 previously, reactive oxygen species are 5 known to be important in development in 6 late stage tumor progression and 7 metastases. 8 Q. Of the ovary? 9 A. In late stage, yes. 10 Q. No, it doesn't say late 11 stage. It just says ovary. 12 A. It says development and 13 progression. That is not initiation. 14 Development is what happens in subsequent 15 stages of cancer development. And so, as 16 I emphasize, ovarian and other tumors may 17 be reflective of roles of late stage 18 cancer development induced by oxidative 19 stress or inflammation. Not causation. 20 (Document marked for 21 identification as Exhibit 22 Mossman-28.) 23 BY MR. SMITH: 24 Q. I marked that previous</p>
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<p>1 reviewed." 2 MR. FROST: Brooke, you go 3 to -- ours doesn't say 16 or 4 whatever. 5 THE WITNESS: No. 6 MR. FROST: It's 283 -- 7 MR. SMITH: I'm sorry. 8 MR. FROST: -- 5. 9 BY MR. SMITH: 10 Q. And if you go down five 11 lines and go to the right, it says, "We 12 reviewed the recent progress." 13 Do you see that? 14 A. "Recent progress towards the 15 potential role." Okay. 16 Q. "We reviewed the recent 17 progress towards the potential role of 18 ROS and associated oxygen" -- excuse 19 me -- "oxidative stress in the 20 carcinogenesis" -- "in carcinogenesis 21 since they are involved in the 22 development and progression of several 23 human cancers, like cervical, breast and 24 ovary."</p>	<p>1 exhibit as 27. I'm going to mark the 2 next exhibit, which is 28. And this is 3 from the National Cancer Institute, 4 Center Data Access System. 5 And it's "Inflammation 6 Markers and Risk of Endometrial and 7 Ovarian Cancer." And this is in a study 8 that is ongoing, and the principal 9 investigator is Nicolas Wentzensen. 10 Do you know who he is? 11 A. No, I've never heard of him. 12 Q. He's deputy branch chief and 13 senior investigator for the NCI division 14 of cancer epidemiology and genetics, 15 clinical genetics branch. 16 Did you know that? 17 A. I didn't. 18 Q. Okay. And here's a study 19 that's ongoing at the NCI. And here is 20 the title and the summary. 21 "Title, Inflammation Markers 22 and Risk of Endometrial and Ovarian 23 Cancer. Epidemiology evidence suggests 24 that chronic inflammation plays an</p>

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<p>1 important role in the pathogenesis of the 2 endometrial and ovarian cancers." 3 Do you agree with that 4 statement? 5 MR. FROST: Objection. 6 THE WITNESS: Yes. In late 7 stage disease. 8 BY MR. SMITH: 9 Q. It says, "An important role 10 in the" -- what does pathogenesis means? 11 A. Pathogenesis means the 12 development of lesions as they go from an 13 initiated cell to later stages of cancer 14 development. So pathogenesis does not 15 encompass causation. It's the 16 development of the tumors over periods of 17 time. So it's the tissue changes that 18 become evidenced after cancers are 19 initiated. 20 Q. "Chronic inflammation can 21 induce rapid cell division, increasing 22 the possibility of replication error, 23 ineffective DNA repair, and subsequent 24 mutation. Risk factors for endometrial</p>	<p>1 MR. FROST: This one was 28, 2 or this one's 29? 3 MR. SMITH: Excuse me. The 4 last one was 28. 5 (Document marked for 6 identification as Exhibit 7 Mossman-29.) 8 BY MR. SMITH: 9 Q. This is 29. This is a 2008 10 article. It says, "Inflammation is a key 11 contributor to ovarian cancer cell 12 seating." 13 Do you see that, Doctor? 14 A. I do. 15 Q. And if you flip to the -- 16 the last page on the conclusion. In the 17 final paragraph, two, four, six, seven 18 lines down. Far right. "Our data in a 19 mouse model are consistent with the 20 concept that most factors implicated in 21 ovarian cancer incidence converge on 22 inflammation as a common denominator." 23 Do you agree or disagree 24 with that statement?</p>
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<p>1 cancer: Unopposed estrogen use, 2 anovulation, polycystic ovarian syndrome, 3 excessive/prolonged menstruation, 4 diabetes and obesity, and conditions 5 associated with ovarian cancer: 6 Ovulation, pelvic inflammatory disease, 7 PCOS, endometriosis and exposure to talc 8 and asbestos are associated with chronic 9 inflammation." 10 Would you agree with that? 11 MR. FROST: Objection. 12 THE WITNESS: Again, this is 13 a -- it looks like a grant 14 application here. A proposed 15 study. And I would not agree with 16 the statement that exposure to 17 talc is associated with chronic 18 inflammation. 19 BY MR. SMITH: 20 Q. Okay. 21 A. No. 22 Q. Let's next go to -- 23 MR. SMITH: That's 24 Exhibit 28.</p>	<p>1 A. A mouse model. Most of the 2 factors... 3 Q. They performed a mouse model 4 in this study. 5 A. Yes. Inflammation is a 6 common denominator of the pathogenesis, 7 especially late stage, and what these 8 individuals are showing is that when 9 cells are seated in metastases, 10 inflammation becomes important. So 11 that's not inconsistent with the role of 12 oxidants or inflammation in late stage 13 development or metastases of cancers, 14 including ovarian. 15 Q. It says, "Our data in a 16 mouse model are consistent with the 17 concept that most of the factors 18 implicated in ovarian cancer incidence 19 converge on inflammation as a common 20 denominator. One successful path to 21 ovarian cancer prevention has been 22 controlling factors that induce 23 inflammation, such as the use of oral 24 contraceptives to suppress ovulation."</p>

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<p>1 Do you agree with that?</p> <p>2 MR. FROST: Objection.</p> <p>3 THE WITNESS: I think there</p> <p>4 are many reasons that oral</p> <p>5 contraceptives become important,</p> <p>6 including estrogen. So it's one</p> <p>7 pathway.</p> <p>8 BY MR. SMITH:</p> <p>9 Q. "Epidemiologic data show</p> <p>10 that aspirin and other nonsteroidal</p> <p>11 antiinflammatory drugs, NSAIDs, can be</p> <p>12 beneficial in the prevention of multiple</p> <p>13 cancers, including ovarian. Although</p> <p>14 factors associated with the increased</p> <p>15 risk of cancer such as aging and</p> <p>16 menopause can't be prevented, the risk</p> <p>17 can be reduced by suppressing</p> <p>18 inflammation."</p> <p>19 Do you agree with that?</p> <p>20 A. Again, I agree with the</p> <p>21 general premise that it -- inflammation</p> <p>22 may be important in late stage disease.</p> <p>23 Q. They don't say late stage</p> <p>24 disease there, Doctor.</p>	<p>1 appeared, or are relevant to causation of</p> <p>2 ovarian cancer by talc.</p> <p>3 Q. Also, I marked as</p> <p>4 Exhibit 30.</p> <p>5 (Document marked for</p> <p>6 identification as Exhibit</p> <p>7 Mossman-30.)</p> <p>8 THE WITNESS: 30 is?</p> <p>9 MR. FROST: It's coming up.</p> <p>10 He hasn't handed it over yet.</p> <p>11 THE WITNESS: Okay.</p> <p>12 MR. SMITH: Another</p> <p>13 interesting copy job.</p> <p>14 BY MR. SMITH:</p> <p>15 Q. You are familiar with this</p> <p>16 study, are you not, Doctor?</p> <p>17 MR. FROST: Is that more</p> <p>18 than one copy or is it --</p> <p>19 MR. SMITH: Here you go.</p> <p>20 MR. FROST: Okay. Thank</p> <p>21 you.</p> <p>22 MR. SMITH: Yeah.</p> <p>23 BY MR. SMITH:</p> <p>24 Q. This was listed in your</p>
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<p>1 MR. FROST: Objection.</p> <p>2 THE WITNESS: No. And they</p> <p>3 don't say causation either.</p> <p>4 They are talking about</p> <p>5 prevention, and there could be</p> <p>6 many ways in which inflammation</p> <p>7 feeds an already established</p> <p>8 tumor.</p> <p>9 BY MR. SMITH:</p> <p>10 Q. Exhibit 29, 28, or 27, were</p> <p>11 they in your -- or 26, were any of those</p> <p>12 in your reference materials that you</p> <p>13 relied on as a basis for your opinion in</p> <p>14 this case?</p> <p>15 A. Say that again slowly.</p> <p>16 Q. Just the exhibits that we</p> <p>17 just went through, 26 through 29, are</p> <p>18 those listed as -- as reference materials</p> <p>19 that form a basis for your opinion in</p> <p>20 this case?</p> <p>21 A. No. As I emphasized, I</p> <p>22 looked at peer-reviewed original data in</p> <p>23 these studies and performed searches with</p> <p>24 talc and asbestos. And none of these</p>	<p>1 updated reference materials, correct?</p> <p>2 A. Yes.</p> <p>3 Q. "Analgesic use" -- "use and</p> <p>4 ovarian cancer risk: An analysis of</p> <p>5 ovarian cancer cohort consortium,"</p> <p>6 Trabert. It's in 2018. This isn't a</p> <p>7 decade ago, is it?</p> <p>8 A. No. It's an update to their</p> <p>9 earlier study.</p> <p>10 Q. And it says conclusions on</p> <p>11 the second page. "This large,</p> <p>12 prospective analysis suggests that women</p> <p>13 who use aspirin daily have a slightly</p> <p>14 lower risk of developing ovarian cancer,</p> <p>15 10 percent lower than infrequent/nonuse,</p> <p>16 similar to the risk reduced" --</p> <p>17 "reduction observed in case-control</p> <p>18 analyses. The observed potential</p> <p>19 elevated risk for ten plus years of</p> <p>20 frequent aspirin and NSAID use require</p> <p>21 further study, but could be due to</p> <p>22 confounding by medical indications for</p> <p>23 use in variation and drug dosing."</p> <p>24 And you reviewed that prior</p>



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<p>1 to your deposition today; is that 2 correct? 3 A. I did. 4 Q. Okay. All right. Let's 5 talk about transmigration. 6 MR. FROST: One second. Do 7 you want to take a quick? 8 MR. SMITH: Sure. 9 MR. FROST: I can use the 10 restroom. 11 THE VIDEOGRAPHER: We're 12 going off the record. The time is 13 2:43. 14 (Short break.) 15 THE VIDEOGRAPHER: We are 16 going back on record. Beginning 17 Media File Number 4. The time is 18 2:54. 19 BY MR. SMITH: 20 Q. Okay. Doctor, this is going 21 to be one of those situations again. I 22 apologize. And I'm -- we can read the 23 front together, but we can't read the 24 back together.</p>	<p>1 But I've gone through and 2 taken quotes out of different studies. 3 You stated earlier that you 4 did not go through the draft screening 5 assessment of Health Canada, correct, 6 when we were talking about inflammation? 7 A. That's correct. 8 Q. And so, the quote, "This 9 evidence of retrograde transport supports 10 the biological plausibility of the 11 association between perineal talc 12 application and ovarian exposure." 13 Would you agree or disagree 14 with that statement? 15 MR. FROST: Objection to 16 form. 17 THE WITNESS: Yeah, I would 18 disagree. There's no evidence of 19 retrograde talc transfer. 20 BY MR. SMITH: 21 Q. And we went over, earlier 22 you had not reviewed Taher, and the quote 23 here, "Particles of talc appeared to 24 migrate into the pelvis and ovarian</p>
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<p>1 And -- 2 MR. SMITH: Here. I'm going 3 to attach this as Exhibit 31. Am 4 I right? 31. 5 (Document marked for 6 identification as Exhibit 7 Mossman-31.) 8 MR. FROST: Yeah, sounds 9 right. I'm just going to -- 10 before you start, same set of 11 actions as last time. We object 12 to using a summary document 13 that -- 14 MR. SMITH: Sure. 15 MR. FROST: -- and we object 16 to you asking any questions about 17 documents without putting it in 18 front of her. 19 BY MR. SMITH: 20 Q. Okay. This is titled, 21 "Biological plausibility, migration and 22 translocation," and what I've done here 23 is -- and there's a back to it and I'm 24 going to show it to you in a second.</p>	<p>1 tissue causing irritation and 2 inflammation." 3 Would you agree or disagree 4 with that quote from Taher? 5 MR. FROST: Objection. 6 THE WITNESS: I would 7 disagree. This has not been shown 8 in -- certainly not in his 9 studies, which are 10 epidemiological. But in terms of 11 other studies as well. 12 BY MR. SMITH: 13 Q. And also in Taher below it, 14 "Transport of talc via peritoneal stroma 15 and presence of ovaries is documented." 16 Are you aware of studies 17 that document that fact? 18 MR. FROST: Objection. 19 THE WITNESS: There are 20 studies documenting talc in 21 ovaries. But not transported talc 22 via peritoneal stroma. 23 BY MR. SMITH: 24 Q. And Schildkraut, is that one</p>

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<p>1 of the reference materials that you 2 relied upon for your opinions in this 3 case? 4 A. I did look at Schildkraut. 5 I don't know whether I listed it or not, 6 but I recall the study. It's an 7 epidemiological study of African-American 8 populations. 9 Q. Yeah, it's not listed in 10 your key references or reliance 11 materials. 12 A. Oh. 13 Q. But you said you read it? 14 A. I -- I have looked at it in 15 the past, yes. 16 Q. And says, quote from that 17 article, "As most high grade serous 18 epithelial ovarian cancer but not 19 nonserous subtypes arise in the fallopian 20 tube. It is possible that direct 21 exposure through genital talc 22 specifically affects this disease 23 subtype." 24 That we had talked earlier</p>	<p>1 BY MR. SMITH: 2 Q. So you don't -- can't answer 3 my question? 4 A. I can't remember. I'd have 5 to go back and look and see whether -- 6 what were the results in terms of certain 7 subtypes of tumors. 8 Q. Well, you had told me 9 earlier that the cohorts which you mainly 10 relied on supported your position that 11 talc does not statistically significantly 12 increase the risk of ovarian cancer. And 13 you can't tell me that one of the -- if 14 one of the cohort studies that you're 15 relying on heavily for that -- for that 16 statement, that it showed that a 17 statistical significant increased risk of 18 a particular type of histology of ovarian 19 cancer? 20 MR. FROST: Objection. 21 THE WITNESS: If I recall 22 the Nurses' Health Study, the 23 original publication emphasized 24 more or a -- that there were more</p>
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<p>1 about high grade serous epithelial 2 ovarian cancer thought to arise in the 3 fallopian tube; is that correct? 4 MR. FROST: Objection. 5 THE WITNESS: That's true. 6 But that statement doesn't, in his 7 report, doesn't support the 8 premise of direct exposure through 9 the genital tract. And it's 10 unclear to me how this would 11 affect specifically one disease 12 subtype. 13 BY MR. SMITH: 14 Q. Well, in the first Nurses' 15 Health Study, what was -- was there a 16 subtype of histological type of 17 epithelial ovarian cancer that showed a 18 statistical significant increased risk 19 from the genital use of talc? 20 MR. FROST: Objection to 21 form. 22 THE WITNESS: I'd have to go 23 back and look at that study 24 specifically.</p>	<p>1 of the serous high grade tumors 2 observed. But that was not of 3 statistical significance. 4 And in the later study, that 5 did not appear to be the case. 6 And I believe it was Gertig versus 7 Gates. But I'd have to go back 8 and look at the studies 9 specifically. 10 BY MR. SMITH: 11 Q. Same from -- and also 12 Schildkraut. Did you realize that 13 Dr. Schildkraut is a female? 14 A. No. 15 Q. Okay. 16 "Therefore, lung inhalation 17 of powder could be a biologically 18 plausible mechanism for the association 19 between nongenital body powder use and 20 the increased risk" -- "increased 21 epithelial ovarian cancer risk, 22 particularly nonserous epithelial ovarian 23 cancers." 24 Do you agree with that</p>

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<p>1 statement from Schildkraut?</p> <p>2 MR. FROST: Objection.</p> <p>3 THE WITNESS: Oh. I don't.</p> <p>4 They did find an increase in</p> <p>5 nongenital body power -- powder</p> <p>6 use, but not genital body powder</p> <p>7 use in that study.</p> <p>8 And other studies have not</p> <p>9 supported the nongenital route as</p> <p>10 being important in -- in ovarian</p> <p>11 cancer risk.</p> <p>12 BY MR. SMITH:</p> <p>13 Q. Well, let me ask you about</p> <p>14 that. Let me attach which is the next</p> <p>15 numbered exhibit, Number 32.</p> <p>16 (Document marked for</p> <p>17 identification as Exhibit</p> <p>18 Mossman-32.)</p> <p>19 BY MR. SMITH:</p> <p>20 Q. I do have those stapled.</p> <p>21 This is entitled,</p> <p>22 "Translocation pathways for inhaled</p> <p>23 asbestos fibers."</p> <p>24 Do you see that, Doctor?</p>	<p>1 subjects exposed to asbestos."</p> <p>2 Do you see that?</p> <p>3 A. Let's see. Is it -- this</p> <p>4 also in the abstract?</p> <p>5 Q. No, it's in the conclusion</p> <p>6 on Page 6 of 8.</p> <p>7 A. Oh, okay.</p> <p>8 Q. It says, "Asbestos fibers</p> <p>9 are found basically in all organs in</p> <p>10 subjects exposed to asbestos."</p> <p>11 Do you see that?</p> <p>12 A. Yes.</p> <p>13 Q. So let's get back to our</p> <p>14 outline that we were going through with</p> <p>15 Schildkraut.</p> <p>16 It says, "It has been</p> <p>17 proposed that chronic inflammation</p> <p>18 resulting from exposure to body powder,</p> <p>19 whether through inhalation or through</p> <p>20 transvaginal route may exert a</p> <p>21 suppressive effect on adaptive immunity</p> <p>22 leading to increased risk of epithelial</p> <p>23 ovarian cancer."</p> <p>24 Do you agree or disagree</p>
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<p>1 It's a 2008 paper, January 2008?</p> <p>2 A. Yes.</p> <p>3 Q. And if you flip to the</p> <p>4 conclusion, on Page 6 of 8. This has to</p> <p>5 do with inhalation and pathways for</p> <p>6 obviously asbestos fibers as it -- it</p> <p>7 talks about.</p> <p>8 In the -- excuse me. Let's</p> <p>9 go to the abstract at the very beginning.</p> <p>10 I'm sorry.</p> <p>11 "We discuss the</p> <p>12 translocation of inhaled asbestos fibers</p> <p>13 based on pulmonary and pleuropulmonary</p> <p>14 interstitial fluid dynamics. Fibers can</p> <p>15 pass the alveolar barrier and reach the</p> <p>16 lung interstitium via the paracellular</p> <p>17 route down a mass water flow due to</p> <p>18 combined osmotic and hydraulic pressure</p> <p>19 gradient."</p> <p>20 Do you see that?</p> <p>21 A. Yes.</p> <p>22 Q. And then in conclusion on</p> <p>23 Page 6 of 8, it says, "Asbestos fibers</p> <p>24 are found basically in all organs in</p>	<p>1 with that statement from Schildkraut?</p> <p>2 MR. FROST: Objection to</p> <p>3 form.</p> <p>4 THE WITNESS: I don't</p> <p>5 believe that a transvaginal</p> <p>6 route -- I'm not sure what is</p> <p>7 meant by that.</p> <p>8 But certainly, whether</p> <p>9 inflammation exerts a suppressive</p> <p>10 effect on adaptive immunity has</p> <p>11 not been shown in ovarian cancer.</p> <p>12 BY MR. SMITH:</p> <p>13 Q. Next paragraph. "The</p> <p>14 results of this study show that genital</p> <p>15 powder use was associated with ovarian</p> <p>16 cancer risk in African-American women,</p> <p>17 and are consistent with localized chronic</p> <p>18 inflammation in the ovary due to</p> <p>19 particles that travel through a direct</p> <p>20 transvaginal route."</p> <p>21 Do you agree or disagree</p> <p>22 with that statement?</p> <p>23 MR. FROST: Objection to</p> <p>24 form.</p>

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<p style="text-align: right;">Page 326</p> <p>1 THE WITNESS: I disagree.</p> <p>2 Dr. Schildkraut did not look at</p> <p>3 the travel of particles to the</p> <p>4 ovary through a direct</p> <p>5 transvaginal route.</p> <p>6 BY MR. SMITH:</p> <p>7 Q. And Houghton was one of the</p> <p>8 cohorts you said that you relied heavily</p> <p>9 on for your opinion that talc does not</p> <p>10 statistically increase the risk of</p> <p>11 ovarian cancer, correct?</p> <p>12 A. Yes.</p> <p>13 Q. And this is a quote from</p> <p>14 Houghton, if you see below that. "Talc</p> <p>15 particulates from perineal application</p> <p>16 have been shown to migrate to the</p> <p>17 ovaries."</p> <p>18 Do you agree or disagree</p> <p>19 with that statement?</p> <p>20 MR. FROST: Objection.</p> <p>21 THE WITNESS: I'd have to</p> <p>22 look at her publication. I know</p> <p>23 she did not look at migration in</p> <p>24 her studies. So I couldn't agree</p>	<p style="text-align: right;">Page 328</p> <p>1 cancer. But not through pathways</p> <p>2 that are linked to translocation</p> <p>3 to the ovaries.</p> <p>4 BY MR. SMITH:</p> <p>5 Q. What are you basing that</p> <p>6 opinion on?</p> <p>7 A. First of all, if you have a</p> <p>8 hysterectomy, you are removing the source</p> <p>9 or the site of tumor development. And</p> <p>10 you're also affecting hormonal states</p> <p>11 which might be important.</p> <p>12 So to extrapolate results</p> <p>13 from tubal ligation or hysterectomy to</p> <p>14 pathways where talc migrates to the</p> <p>15 ovaries can't be linked from these</p> <p>16 studies.</p> <p>17 Q. You -- you said that for</p> <p>18 hysterectomies, but what about tubal</p> <p>19 ligation?</p> <p>20 A. A tubal ligation may do a</p> <p>21 lot of things.</p> <p>22 Q. May?</p> <p>23 A. Yes. There's supplemental</p> <p>24 hormones that maybe have to be given as a</p>
<p style="text-align: right;">Page 327</p> <p>1 with that without seeing the</p> <p>2 reference that supports the fact</p> <p>3 that talc particulates may migrate</p> <p>4 to the ovaries. I have not seen</p> <p>5 data showing that.</p> <p>6 BY MR. SMITH:</p> <p>7 Q. Okay. And to go on in that</p> <p>8 paragraph. "Furthermore, tubal ligation</p> <p>9 and/or hysterectomy which would eliminate</p> <p>10 the pathway of talc particles to the</p> <p>11 ovaries are associated with a reduced</p> <p>12 cancer risk."</p> <p>13 Do you see that?</p> <p>14 MR. FROST: Objection to</p> <p>15 form.</p> <p>16 BY MR. SMITH:</p> <p>17 Q. It's in the same paragraph.</p> <p>18 A. Yes.</p> <p>19 Q. Do you agree or disagree</p> <p>20 with that statement from Houghton?</p> <p>21 MR. FROST: Objection.</p> <p>22 THE WITNESS: I agree with</p> <p>23 the fact that tube ligation and</p> <p>24 hysterectomy would affect ovarian</p>	<p style="text-align: right;">Page 329</p> <p>1 result.</p> <p>2 Q. May have to be given or you</p> <p>3 know this? What -- where are you getting</p> <p>4 this from?</p> <p>5 MR. FROST: Objection.</p> <p>6 THE WITNESS: From my</p> <p>7 experience when I was in the</p> <p>8 department of obstetrics and</p> <p>9 gynecology and working with a</p> <p>10 physician in this regard.</p> <p>11 BY MR. SMITH:</p> <p>12 Q. Wait, hold on. The</p> <p>13 department of obstetrics and gynecology,</p> <p>14 when and where?</p> <p>15 A. At the University of</p> <p>16 Vermont. I mentioned earlier that --</p> <p>17 Q. I understand.</p> <p>18 A. -- that's where I got my</p> <p>19 masters degree in cervical cancer</p> <p>20 induction.</p> <p>21 And I worked with a doctor</p> <p>22 who did a variety of procedures including</p> <p>23 publishing on tubal ligations.</p> <p>24 Q. So when you are getting your</p>

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<p>1 masters, how long of a program was this</p> <p>2 with this doctor?</p> <p>3 A. With Dr. Ray, I started as</p> <p>4 an undergraduate working summers. So I</p> <p>5 would say a total of maybe five years.</p> <p>6 Q. So as an undergraduate and</p> <p>7 as a -- in your masters program, working</p> <p>8 with a doctor who is an OB/GYN and</p> <p>9 observing him do tubal ligations and --</p> <p>10 A. No. That's not what I'm</p> <p>11 saying.</p> <p>12 Q. Well, what --</p> <p>13 A. What I'm saying is that</p> <p>14 tubal ligation occurs because of damage</p> <p>15 to an ovary, infection in the pelvic</p> <p>16 area, including chronic infection. And</p> <p>17 if you remove or tie off the tubes, it's</p> <p>18 a way to curb these various diseases.</p> <p>19 Tubal ligations are not done</p> <p>20 to eliminate pathways of talc migration</p> <p>21 to the ovaries.</p> <p>22 Q. I don't think --</p> <p>23 A. This makes no sense.</p> <p>24 Q. I don't think that's what</p>	<p>1 that's citing studies of women that have</p> <p>2 had tubal ligations and looking at that,</p> <p>3 right?</p> <p>4 The -- the purpose of -- the</p> <p>5 purpose of the -- of the -- the women</p> <p>6 getting the tubal ligation wasn't to</p> <p>7 prevent talc from going to their ovaries,</p> <p>8 but they are looking at reduced cancer</p> <p>9 risk from women that have that in these</p> <p>10 studies, correct?</p> <p>11 MR. FROST: Objection.</p> <p>12 THE WITNESS: What I -- you</p> <p>13 asked if I agreed with the</p> <p>14 statement. And tubal ligation is</p> <p>15 not -- doesn't eliminate the</p> <p>16 pathway of talc particles to the</p> <p>17 ovaries as a primary function of</p> <p>18 the procedure.</p> <p>19 So it's -- this is an</p> <p>20 epidemiological study. We're</p> <p>21 talking about plausible pathways</p> <p>22 of migration or translocation of</p> <p>23 particles to the ovaries. And</p> <p>24 what I'm saying here is that</p>
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<p>1 they are saying. What -- tubal ligation</p> <p>2 can also be used to prevent pregnancy, as</p> <p>3 a form of birth control, right?</p> <p>4 A. Well, it's pretty severe.</p> <p>5 Yes.</p> <p>6 Q. I have heard a woman saying</p> <p>7 she is going to get her tubes tied after</p> <p>8 she has her third child. I've heard that</p> <p>9 routinely, have you not?</p> <p>10 A. Yes, but it also affects</p> <p>11 their hormonal status.</p> <p>12 What I'm saying is there are</p> <p>13 many repercussions to tubal ligations and</p> <p>14 they are not done to eliminate the</p> <p>15 pathway of talc particles to the ovaries.</p> <p>16 Q. I don't think that's what</p> <p>17 they are stating here. I think that</p> <p>18 what --</p> <p>19 A. Well, that's --</p> <p>20 Q. -- Houghton is stating is,</p> <p>21 furthermore, tubal ligation and</p> <p>22 hysterectomy, which would eliminate the</p> <p>23 pathway of talc particles to the ovaries</p> <p>24 are associated with a reduced risk and</p>	<p>1 there's no link between tubal</p> <p>2 ligation, hysterectomy, and</p> <p>3 pathways of talc particle</p> <p>4 migration to the ovaries.</p> <p>5 BY MR. SMITH:</p> <p>6 Q. So you're telling me that if</p> <p>7 the theory is, and what's been stated in</p> <p>8 all of the stuff that I've read with you</p> <p>9 and attached as Exhibit 31, about</p> <p>10 transmigration from a woman dusting her</p> <p>11 perineum with Baby Powder or Shower to</p> <p>12 Shower, and its ascension up the -- the</p> <p>13 genital tract of a woman, through the</p> <p>14 fallopian tubes to the ovaries, that if I</p> <p>15 then ligate the fallopian tubes,</p> <p>16 therefore, preventing an open fallopian</p> <p>17 tube path to the ovary, that that would</p> <p>18 not prevent the passage of talc to the</p> <p>19 ovary?</p> <p>20 MR. FROST: Objection.</p> <p>21 THE WITNESS: There's no</p> <p>22 evidence suggesting that talc</p> <p>23 particles migrate to the ovary, is</p> <p>24 what I'm saying.</p>

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<p>1 BY MR. SMITH: 2 Q. Well, we talked about Taher 3 earlier, the study that you hadn't seen 4 in 2018 regarding Health Canada. Do you 5 recall that? 6 A. That's a meta-analysis of an 7 unpublished paper. He did not look at 8 migration to the ovaries. 9 Q. Okay. And in that study it 10 says, "Women with prior ligation of the 11 fallopian tubes showed a significant 12 reduction in risk against ovarian cancer 13 compared to hysterectomy." And then it 14 says, "In a recent meta-analysis, the 15 authors reported a negative association 16 of tubal ligation (27 studies) and 17 hysterectomy (15 studies) with the risk 18 of ovarian cancer. This negative 19 association was more apparent in women 20 who had surgery at an early stage. A 21 highly plausible mechanism for this 22 association, as suggested by the authors, 23 involves blocking of ascent of agents 24 such as talc to the ovaries."</p>	<p>1 Doctor, have you -- did you rely on 2 Huncharek 2007 and Langseth 2008 for your 3 opinions in this case? 4 A. I did. But not with regard 5 to talc migration to the ovaries, which 6 was not examined in any of these studies. 7 Q. Well, Langseth down here at 8 the bottom, quote, "The evidence of talc 9 migration of the ovaries lends 10 credibility to such a possible 11 association." 12 Would you agree or disagree 13 with that? 14 MR. FROST: Objection. 15 THE WITNESS: I would 16 disagree. His studies did not 17 show talc migration to the 18 ovaries. 19 BY MR. SMITH: 20 Q. Okay. And then we have 21 Mills in 2004, Gertig in -- did you rely 22 on Mills for migration opinions in this 23 case? I'm looking at the -- I'm sorry. 24 MR. FROST: I take it this</p>
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<p>1 Would you agree with that or 2 disagree with that statement from Taher? 3 MR. FROST: Objection. 4 THE WITNESS: I disagree 5 with the statement. There is no 6 evidence supporting a biological 7 plausibility of migration or 8 translocation of talc to the 9 ovaries. In fact, there's a lot 10 of information showing that that 11 doesn't exist. 12 BY MR. SMITH: 13 Q. So you don't believe in 14 retrograde menstruation in women? 15 MR. FROST: Objection. 16 THE WITNESS: I don't 17 believe in it? 18 BY MR. SMITH: 19 Q. Does it not exist? 20 A. It happens in a very small 21 proportion, and that's entirely different 22 than movement of an inert particle 23 through retrograde migration. 24 Q. And we can go through them.</p>	<p>1 is the back side of that sheet? 2 MR. SMITH: Yeah. 3 THE WITNESS: I'm looking. 4 BY MR. SMITH: 5 Q. Mills 2004 for migration in 6 this case? 7 A. Oh, he's -- here Mills is 8 mentioning migration from the vagina 9 through the peritoneal cavity to the 10 ovaries. No, I've never seen anything 11 showing that pathway through a peritoneal 12 cavity from the vagina to the ovaries, 13 no. 14 Q. Okay. And Gertig, did you 15 rely on that for any of your -- 16 A. I relied on it for the 17 epidemiology, not for the statement that 18 talc is able to migrate. 19 Q. And Ness 1999, we discussed 20 that. You've looked at those studies in 21 2000, correct? 22 A. Right. 23 Q. Is that correct? 24 A. That -- that's correct.</p>

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<p>1 Those are outdated, and they're</p> <p>2 hypotheses papers that didn't look at</p> <p>3 migration directly.</p> <p>4 Q. What about Cramer '99 or</p> <p>5 Heller '96?</p> <p>6 A. Cramer found the same amount</p> <p>7 of material in ovarian -- I should say in</p> <p>8 the ovaries of individuals who did use</p> <p>9 and did not use talc. So I would not</p> <p>10 support that. His evidence has just been</p> <p>11 looking at -- by pathology. So I</p> <p>12 would -- he did not perform migration</p> <p>13 studies. Heller also did not.</p> <p>14 Q. You're saying that</p> <p>15 Dr. Cramer in 1999 found talc in people</p> <p>16 exposed and not exposed?</p> <p>17 MR. FROST: Objection.</p> <p>18 THE WITNESS: I have to look</p> <p>19 at -- yeah, that isn't what I</p> <p>20 said. He found that talc -- I</p> <p>21 believe it was talc -- was in</p> <p>22 ovarian tissues, and it didn't</p> <p>23 necessarily correlate with talc</p> <p>24 use. But I'd have to go back and</p>	<p>1 transmigration in this case?</p> <p>2 A. Hamilton, I don't recall</p> <p>3 that paper. I'd have to look at it.</p> <p>4 Q. It says, "There is evidence</p> <p>5 of transport of particulate material into</p> <p>6 the female peritoneum by the transvaginal</p> <p>7 route in both human and animal studies."</p> <p>8 Would you agree or disagree</p> <p>9 with that?</p> <p>10 A. Where are you now? I'm</p> <p>11 sorry.</p> <p>12 No, I don't think that's</p> <p>13 been shown. The presence of talc has</p> <p>14 been shown. It doesn't correlate with</p> <p>15 talc use. But the pathway, if any, is</p> <p>16 unclear, and certainly not from the</p> <p>17 perineum.</p> <p>18 Q. "Direct communication</p> <p>19 between the external environment and the</p> <p>20 peritoneal cavity exist in the female via</p> <p>21 her genital tract."</p> <p>22 Would you agree with that?</p> <p>23 MR. FROST: Objection.</p> <p>24 THE WITNESS: I don't know</p>
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<p>1 look at that.</p> <p>2 BY MR. SMITH:</p> <p>3 Q. It --</p> <p>4 A. I could be confusing that</p> <p>5 with Heller without the papers in front</p> <p>6 of me.</p> <p>7 Q. And Heller '96, have you</p> <p>8 looked at those papers -- that paper,</p> <p>9 excuse me?</p> <p>10 A. I did. And again, it's</p> <p>11 looking at what's there in the ovary and</p> <p>12 not how it got there. And that's true of</p> <p>13 Cramer as well. These are pathology</p> <p>14 studies.</p> <p>15 Q. What about Hamilton 1986?</p> <p>16 MR. FROST: Can you raise</p> <p>17 the sheet?</p> <p>18 MR. SMITH: Yeah.</p> <p>19 MR. FROST: Thanks.</p> <p>20 MR. SMITH: Sure.</p> <p>21 BY MR. SMITH:</p> <p>22 Q. What about Hamilton 1986?</p> <p>23 Have you looked at that, and does that</p> <p>24 form the basis of your opinion about</p>	<p>1 what "communication" means.</p> <p>2 Certainly the genital tract is not</p> <p>3 an open system.</p> <p>4 BY MR. SMITH:</p> <p>5 Q. You don't believe the female</p> <p>6 genital tract is an open system?</p> <p>7 A. I believe that it's -- it's</p> <p>8 not open to the environment, that there</p> <p>9 are a variety of protective mechanisms,</p> <p>10 beginning with the external perineal skin</p> <p>11 and other mechanisms such as the labia,</p> <p>12 and clearance mechanisms through normal</p> <p>13 clearance of the tract.</p> <p>14 Q. "The case of migration of</p> <p>15 particulate material from the vagina to</p> <p>16 the peritoneal cavity has been</p> <p>17 established."</p> <p>18 Do you agree or disagree</p> <p>19 with that quote from Hamilton?</p> <p>20 MR. FROST: Objection.</p> <p>21 THE WITNESS: From the</p> <p>22 vagina, I would have to go back</p> <p>23 and look. But there have been</p> <p>24 studies that have introduced</p>

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<p style="text-align: right;">Page 342</p> <p>1 material into the vagina, 2 particularly in animals that are 3 manipulated. 4 And I think that's what 5 they're talking about here. 6 BY MR. SMITH: 7 Q. So do you believe that if 8 talc is placed into the vagina, that it 9 then can transmigrate through the female 10 genital tract to the ovary? 11 MR. FROST: Objection. 12 THE WITNESS: I have not 13 seen those studies, no. 14 BY MR. SMITH: 15 Q. You haven't seen -- 16 A. Particulate matter. 17 Q. You haven't seen any of the 18 inert particle studies that show any of 19 that testing like -- 20 A. There is one study, I 21 believe, in the 1980s that looks at this 22 in women in a supine position. But these 23 studies that have been done, for example, 24 in rabbits and in monkeys argue against</p>	<p style="text-align: right;">Page 344</p> <p>1 A. It says that retrograde 2 migration was not considered to be 3 plausible by the group, yes. There is a 4 statement on that in the IARC monograph. 5 Q. Okay. Are you familiar with 6 the Phillip's rabbit study that found 7 talc can migrate to the fallopian tubes? 8 Phillips. 9 A. I believe that was one where 10 it was -- it wasn't perineal application. 11 I do remember that study. And it was -- 12 it may have been vaginal or applied 13 directly to the ovary. I'm not certain. 14 There was an earlier study. 15 Q. Is this in your reference 16 materials? I don't see it? 17 A. No, it's in the IARC. Well, 18 I reference the IARC monograph that has a 19 lot of references. And I believe that 20 Phillips is in that one. 21 Q. The Hamilton, last quote, 22 "The rhythmic muscular contractions of 23 the uterus that can occur spontaneous and 24 the elicit current's established" --</p>
<p style="text-align: right;">Page 343</p> <p>1 vaginal or perineal migration of talc to 2 the ovaries. 3 Q. I'm talking about if the 4 talc is placed inside the woman's vagina. 5 I'm not talking about from perineal 6 dusting. And my question is, are you of 7 the opinion that that talc, if placed in 8 the vagina of a woman, can transmigrate 9 to the fallopian tubes in a woman? 10 MR. FROST: Objection. 11 THE WITNESS: My statements 12 would be the same as the IARC 13 concludes on this. And that is, 14 that there's no evidence that this 15 happens in healthy women. That 16 what has been done in terms of the 17 experimental studies have been 18 shown in women with clearance 19 mechanisms that are compromised by 20 infection or other pathologies. 21 BY MR. SMITH: 22 Q. You're saying that IARC, the 23 2010 IARC monograph, says that 24 transmigration does not happen?</p>	<p style="text-align: right;">Page 345</p> <p>1 "established by the epithelial cells of 2 the genital tract may contribute to the 3 translocation process." 4 Do you agree or disagree 5 with that statement? 6 MR. FROST: Objection. 7 THE WITNESS: In normal 8 individuals, this would not be a 9 plausible mechanism. 10 BY MR. SMITH: 11 Q. Are you familiar with the 12 Kuntz studies about the peristolic pump? 13 A. These are the ones where I 14 believe they looked at -- or labeled 15 spermatozoa or other particles. And I 16 know they were discounted by the IARC 17 because of the experimental flaws. 18 Q. I didn't see -- do you have 19 Dr. Cramer and Dr. Godleski's 2007 case 20 study on a woman who was a chronic -- or 21 a long-time genital talc user and their 22 findings of translocation? Have you 23 looked at that article? 24 A. Is it -- if this is a case</p>

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<p>1 report I wouldn't have localized it with</p> <p>2 my searches, no.</p> <p>3 Q. Okay. I'm going to mark</p> <p>4 what's the next exhibit, Number 33.</p> <p>5 (Document marked for</p> <p>6 identification as Exhibit</p> <p>7 Mossman-33.)</p> <p>8 BY MR. SMITH:</p> <p>9 Q. And this is entitled,</p> <p>10 "Correlative polarizing light and</p> <p>11 scanning electron microscopy for the</p> <p>12 assessment of talc in pelvic region" --</p> <p>13 "region lymph nodes." Sandra McDonald is</p> <p>14 the lead author.</p> <p>15 Have you seen this</p> <p>16 article -- or study, excuse me?</p> <p>17 A. I believe I have seen it at</p> <p>18 some point in the past, yes.</p> <p>19 Q. It's not in your materials</p> <p>20 or your updated reference materials?</p> <p>21 A. No. Mainly because these</p> <p>22 are in pelvic lymph nodes, not in the</p> <p>23 ovary. So I would not have included this</p> <p>24 as compelling evidence one way or</p>	<p>1 THE WITNESS: No, but I'm</p> <p>2 talking about the relevance. This</p> <p>3 is looking at talc in lymph nodes.</p> <p>4 I suggest you look at studies by</p> <p>5 Dodson, et cetera, that have</p> <p>6 looked and found particles of all</p> <p>7 different types, including talc,</p> <p>8 in lymph nodes all over the body</p> <p>9 in the general population.</p> <p>10 BY MR. SMITH:</p> <p>11 Q. Well, then how did it get</p> <p>12 there?</p> <p>13 A. I told you that lymph nodes</p> <p>14 are a flow system that collect -- they</p> <p>15 are essentially garbage cans for inhaled</p> <p>16 materials or materials in general.</p> <p>17 Q. I agree. My question to you</p> <p>18 is if talc, and you agree they have been</p> <p>19 found in lymph nodes, they either got</p> <p>20 there through inhalation or ingestion or</p> <p>21 through some other route such as a</p> <p>22 genital -- genital route.</p> <p>23 How did it get -- how did</p> <p>24 talc, in your opinion, get to lymph nodes</p>
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<p>1 another. It's been shown by others that</p> <p>2 any types of particles accumulate in</p> <p>3 lymph nodes all over the body. It's a</p> <p>4 normal mechanism of clearance. So I</p> <p>5 would not give this any relevance,</p> <p>6 certainly not to the development of</p> <p>7 ovarian cancers.</p> <p>8 Q. So have you read this</p> <p>9 article and -- and what it discusses</p> <p>10 about transmigration of particles in</p> <p>11 the -- in the female genital tract?</p> <p>12 A. No, I have not.</p> <p>13 Q. And was this in reliance of</p> <p>14 your materials in forming the basis for</p> <p>15 your opinion about transmigration in this</p> <p>16 case?</p> <p>17 A. No, it would not be relevant</p> <p>18 to ovarian cancers as talc has been found</p> <p>19 in lymph nodes all over the body in the</p> <p>20 normal population.</p> <p>21 Q. Well, that's not it's --</p> <p>22 that's not what it's discussing in this</p> <p>23 paper.</p> <p>24 MR. FROST: Objection.</p>	<p>1 inside human beings if it wasn't by one</p> <p>2 of those routes?</p> <p>3 A. It --</p> <p>4 MR. FROST: Objection.</p> <p>5 THE WITNESS: It would be</p> <p>6 primarily by inhalation. We know</p> <p>7 that. And ingestion. Talc is in</p> <p>8 a lot of different food processes.</p> <p>9 It's in plastics. We're all</p> <p>10 exposed to it.</p> <p>11 BY MR. SMITH:</p> <p>12 Q. Have you ever read the FDA's</p> <p>13 response to citizen's petition on talc?</p> <p>14 A. No. That -- I never would</p> <p>15 have found that in the scientific</p> <p>16 literature.</p> <p>17 Q. It says, "While there exists</p> <p>18 no direct proof of talc and ovarian</p> <p>19 carcinogenesis, the potential for</p> <p>20 particulates to migrate from the perineum</p> <p>21 and vagina to the peritoneal cavity is</p> <p>22 indisputable."</p> <p>23 Do you agree or disagree</p> <p>24 with that?</p>

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<p>1 MR. FROST: Objection.</p> <p>2 THE WITNESS: I would assume</p> <p>3 that this report is -- or letter</p> <p>4 is from an individual. Certainly</p> <p>5 no balanced committee would make</p> <p>6 that statement.</p> <p>7 BY MR. SMITH:</p> <p>8 Q. Okay. "It is, therefore,</p> <p>9 plausible that perineal talc and other</p> <p>10 particulate that reaches the endometrial</p> <p>11 cavity, fallopian tubes and ovaries may</p> <p>12 elicit a foreign body-type reaction and</p> <p>13 inflammatory that" -- "response that in</p> <p>14 some exposed women may progress to</p> <p>15 epithelial ovarian cancers."</p> <p>16 Do you agree or disagree</p> <p>17 with that statement?</p> <p>18 MR. FROST: Objection.</p> <p>19 THE WITNESS: I think it's</p> <p>20 hypotheses. It's unproven and I'm</p> <p>21 sure a committee would not have</p> <p>22 made that statement.</p> <p>23 BY MR. SMITH:</p> <p>24 Q. I want to talk about your</p>	<p>1 quantitating exposure of different</p> <p>2 materials to cells and culture, is based</p> <p>3 on their surface area determinations</p> <p>4 because it's the surface area that</p> <p>5 governs their interaction with the cell</p> <p>6 surface.</p> <p>7 Q. Okay. And you did a</p> <p>8 conversion, did you not? It's -- do you</p> <p>9 have the Hillegass study by any chance?</p> <p>10 Probably not. Let me grab it for you.</p> <p>11 MR. FROST: Do you have one?</p> <p>12 MR. SMITH: Yeah, I got it.</p> <p>13 (Document marked for</p> <p>14 identification as Exhibit</p> <p>15 Mossman-34.)</p> <p>16 BY MR. SMITH:</p> <p>17 Q. I notice one of the comments</p> <p>18 to -- and let's go to that right now. I</p> <p>19 have got that over here. Now we might be</p> <p>20 branching out to this guy here. I don't</p> <p>21 know.</p> <p>22 If we look at the front of</p> <p>23 the second page. It says -- this is</p> <p>24 reviewers to the study. Do you see that,</p>
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<p>1 Shukla study. Is that okay?</p> <p>2 A. Sure.</p> <p>3 Q. Do you -- you don't -- do</p> <p>4 you have a copy of it?</p> <p>5 MR. FROST: Yeah, I was</p> <p>6 going to say we don't have a copy.</p> <p>7 MR. SMITH: Yeah. Hold on.</p> <p>8 (Whereupon, a discussion was</p> <p>9 held off the record.)</p> <p>10 BY MR. SMITH:</p> <p>11 Q. Okay. Why did you use the</p> <p>12 concentrations that you did in this</p> <p>13 study, or why did y'all?</p> <p>14 A. Okay. So we were -- we were</p> <p>15 interested in the study in comparing</p> <p>16 various materials or particles, fibers,</p> <p>17 at equal surface area concentrations.</p> <p>18 And we also expressed the data as equal</p> <p>19 weight concentrations. So that we</p> <p>20 compare it historically to concentrations</p> <p>21 of materials used by others in other</p> <p>22 studies.</p> <p>23 So it's been shown that the</p> <p>24 best method of dosimetry, that is, of</p>	<p>1 Doctor? This is what you provided to me.</p> <p>2 A. Right. Okay.</p> <p>3 Q. Okay. I'm going to attach</p> <p>4 that -- excuse me. Hold on. I'm going</p> <p>5 to attach that as exhibit -- let's attach</p> <p>6 Shukla as Exhibit 34.</p> <p>7 (Document marked for</p> <p>8 identification as Exhibit</p> <p>9 Mossman-35.)</p> <p>10 MR. SMITH: Let's do</p> <p>11 Hillegass as 35. And then this</p> <p>12 collective exhibit of reviewer</p> <p>13 comments with the cover letters,</p> <p>14 it's May 8, 2009, University of</p> <p>15 Vermont, with Jedd Hillegass on</p> <p>16 the bottom.</p> <p>17 (Document marked for</p> <p>18 identification as Exhibit</p> <p>19 Mossman-36.)</p> <p>20 BY MR. SMITH:</p> <p>21 Q. And this is from a reviewer.</p> <p>22 Methods, Page 6. "The dose of minerals</p> <p>23 expressed as surface-based concentration</p> <p>24 may not be intuitive to all readers. As</p>

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<p style="text-align: right;">Page 354</p> <p>1 in the recent publication, Shukla, it 2 would be helpful if some information is 3 provided about the surface area of the 4 various minerals tested, as well as how 5 this translates into micrograms per 6 centimeter squared," right? 7 A. Yes. 8 Q. And then your response or 9 y'all's response was, "Additional 10 information regarding the surface area of 11 particulates used in these studies was 12 added to the methods section along with 13 how many micrograms squared per 14 centimeter squared translates into 15 micrograms per centimeter squared." 16 Right? 17 A. Okay. So I'm trying to 18 figure out whether this is with regard to 19 the Hillegass study; is that correct? 20 Q. Correct. 21 A. Okay. 22 Q. All right. This is my 23 question. 24 A. Sure.</p>	<p style="text-align: right;">Page 356</p> <p>1 Q. If I'm looking at asbestos 2 below at 15 micrometers squared per 3 centimeter squared, how many -- what 4 would that translate to to micrograms per 5 centimeter squared? 6 A. Micrograms, it would -- 7 Okay. So that would equal one. 8 Q. 15 would be one, right? 9 A. With asbestos. 10 Q. Right. And 75 would be -- 11 A. 75 would be five. 12 Q. Five, okay. 13 A. And 15 would be 14 approximately -- well, it's 16.2, would 15 be one with talc. And it would be, again 16 in the same range, 75 versus 81 talc. 17 So we're actually adding 18 talc at higher surface concentrations but 19 fractionally so, as compared to asbestos. 20 Q. My question is, would the 15 21 micrometers squared per centimeter 22 squared for talc that you used the 23 concentration of in this case, would that 24 equal one microgram per centimeter</p>
<p style="text-align: right;">Page 355</p> <p>1 Q. The concentrations that you 2 used, that being -- and I'm talking about 3 Shukla. I'm talking about 34 -- 4 15 micrometers squared per centimeter 5 squared and 75 micrometers squared per 6 centimeter squared, would translate to 7 what micrograms per centimeter squared? 8 A. Okay. And that's -- if you 9 look at Figure 2 in Shukla, Page 4 of 10. 10 Q. Yep. 11 A. And the top panel, you'll 12 see the vertical and the horizontal. And 13 if we look at asbestos and talc, you can 14 see here that the upper column, going 15 from 015 and from talc 15, et cetera, 16 that is the comparative weight per -- so 17 it's weight per unit area of dish. 18 So that's your weight 19 concentration. 20 The numbers below are your 21 surface area concentrations. 22 Q. Okay. So let's get on the 23 same page. 24 A. Mm-hmm.</p>	<p style="text-align: right;">Page 357</p> <p>1 squared? 2 A. Approximately, yes. 3 Q. Okay. That's what I 4 thought. 5 A. Yes. They're comparable. 6 Q. Okay. And 75 micrograms per 7 centimeter squared -- micrograms squared 8 per centimeter squared would equal five 9 micrograms per centimeter squared, right? 10 A. Yes. 11 Q. Okay. Now I'm on the same 12 page. That's what I needed. 13 A. Okay. 14 Q. All right. And do you 15 believe that those concentrations are 16 appropriate to use in in vitro studies to 17 determine the pathogenicity of minerals 18 such as talc and asbestos? 19 A. Yes. And that's based upon 20 the toxicity data that is provided in A 21 and B. So they're comparable 22 concentrations. The asbestos as we can 23 see at five, was toxic and the talc was 24 not. So we -- and you can see that in</p>



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<p>1 the dose-response that we did with five 2 concentrations of talc ranging from one 3 to 20. 4 Q. Okay. So talc you tested at 5 one microgram per centimeter squared, 6 five micrograms per centimeter squared, 7 ten micrograms per centimeter squared, 8 and 20 microgram per centimeter squared? 9 A. 15 and 20. 10 Q. 10, 15, and 20? 11 A. Yes. 12 Q. Okay. 13 A. So the message is that you 14 don't want to work with something that's 15 going to kill all the cells, so you can't 16 go higher. And in fact, that's a reason 17 that with time, we didn't look at the 18 higher concentration of asbestos. 19 Q. I want to attach this as 20 Exhibit 27 so I won't forget this. 21 Because I could. 22 (Document marked for 23 identification as Exhibit 24 Mossman-37.)</p>	<p>1 A. They only sponsored a very 2 small fraction of the studies that were 3 done with the talc. The other materials 4 and the other work was supported by a 5 grant from the National Institutes of 6 Health. 7 Q. Is it unusual to give 8 progress reports to those who sponsor 9 research? 10 A. No. It's demanded from NIH, 11 for example. In other -- in our 12 institution it is. 13 Q. It is -- is it -- it is not 14 unusual to submit proposal to industry 15 involved in regulatory and/or litigation 16 issues, correct? 17 A. Could you say that again. 18 MR. FROST: Objection. 19 BY MR. SMITH: 20 Q. Sure. It is not unusual to 21 submit proposals to industry involved in 22 regulatory and/or litigation issues? 23 MR. FROST: Objection. 24 BY MR. SMITH:</p>
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<p>1 BY MR. SMITH: 2 Q. Here we are, Shukla, 3 "Appropriate Concentration Levels to 4 Determine Pathogenicity of Asbestos and 5 Talc." And this study used concentration 6 levels of talc, at one, five, 10, 15, 7 20 micrograms per centimeter squared, 8 correct? 9 A. Yes. 10 MR. SMITH: Okay. That's 11 Exhibit 37. 12 BY MR. SMITH: 13 Q. Okay. You provided, as we 14 discussed, progress reports to the IMA 15 during the course of this study; is that 16 correct? 17 A. After a year, yes. We 18 didn't provide them with progress 19 reports. I wrote them e-mails that the 20 asbestos data was positive, but the other 21 data didn't appear to be with regard to 22 the other materials. 23 Q. And they sponsored the 24 study, correct, along with EUROTALC?</p>	<p>1 Q. Is that unusual to submit 2 proposals to industry that might be 3 involved in regulatory and/or litigation 4 issues? 5 A. To my knowledge, these 6 institutions were not involved in 7 litigation in 2005. All this work was 8 done prior to litigation ensuing in this 9 country. 10 Q. No, no, I'm just talking in 11 general. I'm not talking about 12 specifically this case. I'm not talking 13 about talc litigation. I'm not talking 14 about any particular litigation. 15 A. Fine. 16 Q. I'm just talking in general 17 terms, it is not unusual to submit 18 proposals to industry involved -- that 19 may be involved in regulatory and/or 20 litigation issues, is it? 21 MR. FROST: Objection. 22 THE WITNESS: It is not 23 unusual in toxicology to submit 24 proposals to industry as that is</p>

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<p>1 where most toxicologists reside.</p> <p>2 BY MR. SMITH:</p> <p>3 Q. And conflicts of interest,</p> <p>4 as far as being expert witness,</p> <p>5 disclosures are up to the specific</p> <p>6 journal, correct?</p> <p>7 A. Yes.</p> <p>8 Q. Okay.</p> <p>9 A. Yes.</p> <p>10 Q. And what do you think the</p> <p>11 study shows regarding talc -- talc's</p> <p>12 carcinogenicity?</p> <p>13 MR. FROST: Objection.</p> <p>14 THE WITNESS: We weren't</p> <p>15 attempting to show changes with</p> <p>16 talc carcinogenicity.</p> <p>17 Let me emphasize that our</p> <p>18 intent in these studies and the</p> <p>19 focus was on asbestos, on</p> <p>20 crocidolite asbestos, what gene</p> <p>21 changes it induced in primarily</p> <p>22 mesothelial cells, as we didn't</p> <p>23 get any striking results in</p> <p>24 ovarian epithelial cells.</p>	<p>1 was unaware of their involvement.</p> <p>2 BY MR. SMITH:</p> <p>3 Q. Would you agree that the</p> <p>4 Shukla study showed that the</p> <p>5 non-pathogenic minerals, glass beads, and</p> <p>6 fine titanium dioxide treatment to cells</p> <p>7 resulted in no gene changes, and</p> <p>8 crocidolite asbestos caused the maximum</p> <p>9 number of gene changes followed by talc?</p> <p>10 A. No, I couldn't say that</p> <p>11 statistically. Based on the statistical</p> <p>12 assays that were performed here, as well</p> <p>13 as in the Hillegass paper, showed that</p> <p>14 the magnitude and the types of gene</p> <p>15 changes were different with talc and</p> <p>16 asbestos, but talc was comparable in</p> <p>17 numbers and types of changes to glass</p> <p>18 beads and titanium dioxide.</p> <p>19 Q. You told me that you did not</p> <p>20 study talc in the Hillegass study.</p> <p>21 MR. FROST: Objection.</p> <p>22 THE WITNESS: I didn't</p> <p>23 say --</p> <p>24 BY MR. SMITH:</p>
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<p>1 And talc was just one of</p> <p>2 other materials that were used to</p> <p>3 see whether our effects were</p> <p>4 specific to a pathogenic mineral</p> <p>5 type or induced by other materials</p> <p>6 as well. And so we used three</p> <p>7 different controls, including talc</p> <p>8 in these studies.</p> <p>9 BY MR. SMITH:</p> <p>10 Q. You're saying talc was used</p> <p>11 as a control?</p> <p>12 A. It turned out to be a</p> <p>13 control, yes. We used it as a control of</p> <p>14 a mineral that was not associated with</p> <p>15 the development of mesothelioma as was</p> <p>16 crocidolite asbestos.</p> <p>17 Q. But at that time, it was</p> <p>18 associated with the possibility of</p> <p>19 increasing the risk in causing ovarian</p> <p>20 cancer, according to IARC, correct?</p> <p>21 MR. FROST: Objection.</p> <p>22 THE WITNESS: No. These</p> <p>23 studies were done in 2005. If</p> <p>24 IARC was involved at that point, I</p>	<p>1 Q. It wasn't tested, talc was</p> <p>2 not tested in the Hillegass study.</p> <p>3 MR. FROST: Objection.</p> <p>4 THE WITNESS: Talc is in the</p> <p>5 data. I'm sorry.</p> <p>6 BY MR. SMITH:</p> <p>7 Q. I understand that, but you</p> <p>8 did not perform all of the tests that you</p> <p>9 did for asbestos. You did not -- you did</p> <p>10 not -- the utilization of gene profiling</p> <p>11 and proteomics to determine mineral</p> <p>12 pathogenicity in a human mesothelial cell</p> <p>13 line. You did not do gene profiling and</p> <p>14 proteomics on talc.</p> <p>15 A. We did. And we had looked</p> <p>16 at it -- we did it in the Shukla study,</p> <p>17 and we looked at the microarray data by</p> <p>18 something called principle component</p> <p>19 analysis in the Hillegass study and</p> <p>20 showed that the changes with talc were</p> <p>21 different in the two different cell</p> <p>22 types, and they were different in</p> <p>23 magnitude and types of gene changes from</p> <p>24 asbestos, and that's in the first figure</p>

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<p>1 in the Hillegass study.</p> <p>2 Q. Oh, we'll -- we'll get to</p> <p>3 the Hillegass study in a minute.</p> <p>4 A. Okay.</p> <p>5 Q. Let's -- let's stick with</p> <p>6 Shukla. All right. I marked -- I marked</p> <p>7 the next -- well, I'm going to mark the</p> <p>8 next exhibit as 38.</p> <p>9 (Document marked for</p> <p>10 identification as Exhibit</p> <p>11 Mossman-38.)</p> <p>12 BY MR. SMITH:</p> <p>13 Q. And this on the NCBI, which</p> <p>14 is the public access of studies, and it</p> <p>15 says status public on September 19, 2011,</p> <p>16 "Alterations in gene expression in human</p> <p>17 mesothelial cells, correlate with mineral</p> <p>18 pathogenicity, organisms, homo sapiens,"</p> <p>19 this is your study we are talking about,</p> <p>20 the Shukla, correct?</p> <p>21 A. It is. Yes.</p> <p>22 Q. Okay. And this is just a</p> <p>23 publication -- a public publication of</p> <p>24 this study, of the summary and overall</p>	<p>1 dioxide treatment to cell resulted in no</p> <p>2 gene changes, crocidolite asbestos caused</p> <p>3 the maximum number of gene changes</p> <p>4 followed by talc."</p> <p>5 And you told me that that</p> <p>6 study, Shukla, did not state that.</p> <p>7 Why would Jeffrey Bond state</p> <p>8 that in the overall design in this</p> <p>9 publication released to the public if</p> <p>10 you're saying the study doesn't reveal</p> <p>11 that in Shukla?</p> <p>12 MR. FROST: Objection.</p> <p>13 THE WITNESS: Yeah. We</p> <p>14 looked at the statistics which are</p> <p>15 not referenced here. And I'm not</p> <p>16 sure why he would have put -- not</p> <p>17 included the statistics.</p> <p>18 But it's important to note</p> <p>19 that the statistical changes by</p> <p>20 talc were not significantly</p> <p>21 elevated as compared to the</p> <p>22 controls which were titanium</p> <p>23 dioxide and glass beads.</p> <p>24 And that was certainly the</p>
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<p>1 design and contributors and citations.</p> <p>2 And I want to look at the overall design.</p> <p>3 But let me ask you first.</p> <p>4 Who is Jeffrey Bond?</p> <p>5 A. Jeffrey Bond is director of</p> <p>6 the biostatistics department within our</p> <p>7 cancer center at the University of</p> <p>8 Vermont. So he was the one who did the</p> <p>9 statistics on these studies.</p> <p>10 Q. And if you look at the</p> <p>11 second page, he's listed as the contact</p> <p>12 name. It says, "Organization, University</p> <p>13 of Vermont; department, microbiology and</p> <p>14 molecular genetics."</p> <p>15 Do you see that, in</p> <p>16 Burlington, Vermont?</p> <p>17 A. Yes.</p> <p>18 Q. And it says, "Overall</p> <p>19 design" -- it says, "Summary," and then</p> <p>20 it says, "Overall design."</p> <p>21 In the last sentence of</p> <p>22 overall design of this study, the Shukla</p> <p>23 study, it says, "While nonpathogenic</p> <p>24 minerals, glass beads and fine titanium</p>	<p>1 case following up with even more</p> <p>2 sophisticated assays in the</p> <p>3 Hillegass paper.</p> <p>4 BY MR. SMITH:</p> <p>5 Q. But you did not look at</p> <p>6 talc, the higher concentrations, at</p> <p>7 24 hours to determine if it was dose</p> <p>8 dependent just like asbestos.</p> <p>9 MR. FROST: Objection to</p> <p>10 form.</p> <p>11 THE WITNESS: You are wrong.</p> <p>12 We looked at eight hours at a low</p> <p>13 and high concentration of talc.</p> <p>14 It certainly was dose dependent.</p> <p>15 We found only one gene at the</p> <p>16 lower concentrations, and 30 at</p> <p>17 the highest.</p> <p>18 BY MR. SMITH:</p> <p>19 Q. Okay.</p> <p>20 A. When we took out the</p> <p>21 experiment to 24 hours at low</p> <p>22 concentrations of both materials, we saw</p> <p>23 that changes with asbestos increased and</p> <p>24 the talc at the lowest concentration did</p>

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<p>1 not result in a higher number. 2 So we certainly did do 3 dose-response experiments. 4 Q. Point me into the Shukla 5 study where you tested talc at the higher 6 concentration on peritoneal mesothelial 7 cells at 24 hours. 8 MR. FROST: Objection. 9 THE WITNESS: I'm saying we 10 didn't look at 24 hours -- 11 BY MR. SMITH: 12 Q. Thank you. 13 A. -- because our cells were 14 dead. 15 Q. Where does that state there? 16 Where is it stated? 17 A. Where? In the paper? 18 Q. That the cells were dead. 19 A. All you have to do is look 20 at the asbestos results -- 21 Q. No, ma'am. I'm talking 22 about for talc. 23 A. We -- we wouldn't have 24 looked -- we wouldn't have looked at talc</p>	<p>1 did cause an increase. 2 MR. SMITH: Again, I'm going 3 to object as nonresponsiveness. 4 BY MR. SMITH: 5 Q. My question is simple and 6 it's easy and clean and neat. 7 Point me to where in the 8 paper at high -- the higher 9 concentration, that you exposed talc to 10 peritoneal mesothelial cells that you say 11 line the fallopian tubes, ovaries and 12 peritoneal cavity at 24 hours. Tell me 13 where you did that. 14 MR. FROST: Objection. 15 THE WITNESS: Let's go 16 back -- 17 BY MR. SMITH: 18 Q. No, ma'am. I need an answer 19 to the question. Did -- tell me in the 20 paper. Show it to me. 21 Where did you expose at 22 24 hours -- 23 A. Why -- 24 Q. Ma'am, let me finish my</p>
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<p>1 without looking at asbestos. Our focus 2 was on asbestos. Why would I look at 3 talc when I couldn't compare it to 4 asbestos? 5 Q. Because I don't have a 6 problem with you making assumptions about 7 asbestos in this paper. The problem I've 8 got is you making assumptions that -- 9 that deal with ovarian issues and ovarian 10 gene expression changes, and what this 11 study says about exposure of talc to 12 peritoneal mesothelial cells. 13 And my question is this: 14 Did you test talc at the higher 15 concentration with peritoneal mesothelial 16 cells at 24 hours, yes or no? 17 MR. FROST: Objection. 18 THE WITNESS: We did not. 19 We looked at the low 20 concentrations of both asbestos 21 and talc at comparable 22 concentrations and showed that 23 talc changes did not increase over 24 time, but asbestos concentrations</p>	<p>1 question. I'm just going to ask a 2 question. 3 Where -- point me in the 4 paper where you exposed peritoneal 5 mesothelial cells to talc at the higher 6 concentrations at 24 hours, point it to 7 me. 8 MR. FROST: Objection. 9 THE WITNESS: We -- we did 10 not look at asbestos or talc at 11 24 hours at the higher 12 concentrations because the cells 13 were dying from asbestos. That's 14 why. 15 BY MR. SMITH: 16 Q. But you don't know if they 17 would have died from talc at 24 hours? 18 MR. FROST: Objection. 19 THE WITNESS: It wouldn't 20 have made any difference. 21 BY MR. SMITH: 22 Q. Sure it would have, because 23 then we could sit here and say, regarding 24 ovarian cells -- peritoneal --</p>

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<p>1 peritoneal -- excuse me, peritoneal</p> <p>2 mesothelial cells that line the ovary and</p> <p>3 fallopian tubes and peritoneal cavity,</p> <p>4 whether there was a dose-dependent</p> <p>5 reaction because you saw 30 genes changes</p> <p>6 at eight hours. And if the gene</p> <p>7 expression would have gone up at 24, then</p> <p>8 we could say there was a dose-dependent</p> <p>9 reaction there?</p> <p>10 MR. FROST: Objection.</p> <p>11 THE WITNESS: No. I want to</p> <p>12 emphasize that we looked at two</p> <p>13 concentrations of talc and</p> <p>14 asbestos at eight hours and there</p> <p>15 was a dose-dependent change with</p> <p>16 asbestos that was of a huge</p> <p>17 magnitude.</p> <p>18 That was not the case with</p> <p>19 talc. And the results were</p> <p>20 essentially the same as we got</p> <p>21 with the other control particles.</p> <p>22 BY MR. SMITH:</p> <p>23 Q. Okay. Well, tell me -- show</p> <p>24 me in this paper where -- I don't see the</p>	<p>1 beads.</p> <p>2 BY MR. SMITH:</p> <p>3 Q. Well, hold on. Show me. If</p> <p>4 you're going to -- if you're going to</p> <p>5 make general statements like that about</p> <p>6 this study, I have charts. I can look at</p> <p>7 them. I can look at the 30 genes that</p> <p>8 were changed and altered at eight hours</p> <p>9 at the higher concentrations of</p> <p>10 peritoneal mesothelial cells by talc.</p> <p>11 You're now making a</p> <p>12 statement that I don't see anywhere in</p> <p>13 this paper that titanium dioxide and</p> <p>14 glass beads did had similar gene changes</p> <p>15 and acted in a similar way that talc did</p> <p>16 compared to mesothelial cells at this</p> <p>17 concentration at these hours.</p> <p>18 And my question is, where is</p> <p>19 that table?</p> <p>20 MR. FROST: Objection.</p> <p>21 THE WITNESS: Of controlled</p> <p>22 gene changes? There weren't any</p> <p>23 significant gene changes.</p> <p>24 BY MR. SMITH:</p>
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<p>1 chart for all the genes -- all the genes</p> <p>2 altered by the exposure to titanium</p> <p>3 dioxide and glass beads.</p> <p>4 A. They were --</p> <p>5 Q. I see a chart for all the</p> <p>6 genes altered by crocidolite asbestos to</p> <p>7 peritoneal mesothelial cells. I see the</p> <p>8 table of non-fibrous talc to peritoneal</p> <p>9 mesothelial cells and 30 genes change.</p> <p>10 I need -- where is -- show</p> <p>11 me where the chart is that titanium</p> <p>12 dioxide and glass beads changed the</p> <p>13 comparable amount of genes that talc</p> <p>14 compared to mesothelial cells at higher</p> <p>15 concentrations --</p> <p>16 MR. FROST: Objection.</p> <p>17 THE WITNESS: They didn't</p> <p>18 cause any increases in more than</p> <p>19 twofold of -- and if you look at</p> <p>20 the data with talc, even with the</p> <p>21 30, we're talking about looking at</p> <p>22 thousands of genes. That number</p> <p>23 statistically is as low as the</p> <p>24 titanium dioxide or the glass</p>	<p>1 Q. Thank you. Thank you.</p> <p>2 And --</p> <p>3 A. That is my point.</p> <p>4 Q. Okay. And let's look at</p> <p>5 Hillegass.</p> <p>6 A. Okay.</p> <p>7 Q. Number 35. You have</p> <p>8 chrysotile asbestos, which you would</p> <p>9 agree with me is carcinogenic, correct?</p> <p>10 A. I didn't use chrysotile</p> <p>11 asbestos in these studies.</p> <p>12 Q. My question to you, is</p> <p>13 chrysotile asbestos carcinogenic?</p> <p>14 MR. FROST: Objection.</p> <p>15 THE WITNESS: I think we</p> <p>16 went through this previously. But</p> <p>17 if you talk about mesothelioma,</p> <p>18 there's a debate on whether the</p> <p>19 risk is zero or one or a low</p> <p>20 number.</p> <p>21 BY MR. SMITH:</p> <p>22 Q. Does IARC and the National</p> <p>23 Toxicology Program consider all types of</p> <p>24 asbestos, including chrysotile, human</p>



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<p>1 carcinogens?</p> <p>2 MR. FROST: Objection.</p> <p>3 THE WITNESS: And that's</p> <p>4 based on lung cancers and</p> <p>5 mesothelioma. And yes, they do.</p> <p>6 BY MR. SMITH:</p> <p>7 Q. Okay. Here, seven</p> <p>8 micrograms per centimeter squared, do you</p> <p>9 see that, Doctor? Of chrysotile. This</p> <p>10 is on your Table 3 of another study,</p> <p>11 correct?</p> <p>12 A. Okay. You are going to have</p> <p>13 to tell me what page that's on.</p> <p>14 Q. It's 18 of 18.</p> <p>15 A. Okay. Okay. This is a</p> <p>16 summary of work done by others in</p> <p>17 comparison to our work.</p> <p>18 Q. Okay. And in the Shukla</p> <p>19 study the higher concentration is</p> <p>20 75 micrometers squared per centimeter</p> <p>21 squared would be five micrograms per</p> <p>22 centimeter squared, correct?</p> <p>23 A. Yes.</p> <p>24 Q. Okay. So the concentration</p>	<p>1 Therefore, we just talked</p> <p>2 about the concentration that you used in</p> <p>3 Shukla of talc would be five micrograms</p> <p>4 per centimeter squared or a lower</p> <p>5 concentration than is used for chrysotile</p> <p>6 on this chart, correct?</p> <p>7 MR. FROST: Objection.</p> <p>8 THE WITNESS: Yeah. I'm not</p> <p>9 sure what you're getting at here.</p> <p>10 BY MR. SMITH:</p> <p>11 Q. Well --</p> <p>12 A. Let me just double-check</p> <p>13 what you're saying, because I'm not sure</p> <p>14 it makes sense.</p> <p>15 Q. We've been through this in</p> <p>16 Brower.</p> <p>17 A. That's what I'm reiterating.</p> <p>18 It didn't make sense either then. Okay.</p> <p>19 Q. Well, let's just agree on</p> <p>20 fundamentals. I mean, it's pretty easy.</p> <p>21 The higher concentration of five -- 75</p> <p>22 micrometers per centimeter squared that</p> <p>23 you used in Shukla for talc equals five</p> <p>24 micrograms per centimeter squared,</p>
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<p>1 that you used of talc in Shukla is lower</p> <p>2 than the concentration here of</p> <p>3 chrysotile, seven micrograms per</p> <p>4 centimeter squared. And the results of</p> <p>5 the study as far as genes altered at four</p> <p>6 hours were eight by chrysotile, correct?</p> <p>7 A. Yes.</p> <p>8 Q. And at eight hours in talc</p> <p>9 at a lower concentration, how many genes</p> <p>10 were upregulated?</p> <p>11 A. In our studies?</p> <p>12 Q. Yes.</p> <p>13 A. One gene was the ATF3 --</p> <p>14 Q. Ma'am --</p> <p>15 A. -- at the lowest</p> <p>16 concentration.</p> <p>17 Q. Ma'am, I'm talking about --</p> <p>18 I'm talking about -- I'm talking about</p> <p>19 the concentration used at the higher</p> <p>20 concentration in your study equals five</p> <p>21 micrograms per centimeter squared. The</p> <p>22 chrysotile that's on this table is seven</p> <p>23 micrograms per centimeter squared as the</p> <p>24 concentration.</p>	<p>1 correct?</p> <p>2 A. In talc, the concentration</p> <p>3 of five micrograms per centimeter squared</p> <p>4 with talc equaled -- I'm sorry, yeah --</p> <p>5 equals 81 surface area. Okay.</p> <p>6 Q. So five micrograms per</p> <p>7 centimeter squared.</p> <p>8 A. Yes.</p> <p>9 Q. Okay. So we're looking --</p> <p>10 this study that you cite in Hillegass for</p> <p>11 chrysotile that IARC and NTP say is</p> <p>12 carcinogenic to humans, uses two</p> <p>13 micrograms per centimeter squared higher</p> <p>14 concentration than you used for talc at</p> <p>15 the higher concentration in Shukla, and</p> <p>16 eight -- excuse me -- at four hours, how</p> <p>17 many genes were altered for chrysotile?</p> <p>18 MR. FROST: Objection to</p> <p>19 form.</p> <p>20 THE WITNESS: Eight. But</p> <p>21 let me emphasize.</p> <p>22 BY MR. SMITH:</p> <p>23 Q. No, ma'am. I don't have a</p> <p>24 question. The question I asked, and how</p>

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<p>1 many genes were upregulated by talc at a 2 lower concentration at eight hours? 30, 3 correct? 4 A. Right. So are you 5 implicating that the results here with a 6 completely different cell type are 7 relevant to what I did in human 8 mesothelial cells or ovarian epithelial 9 cells? 10 Q. Ma'am, you're trying to 11 extrapolate all your work in asbestos to 12 ovarian cancer and what talc's effect on 13 cells that have to do with ovarian 14 cancer. 15 A. I'm sorry, sir -- 16 MR. FROST: Objection. 17 THE WITNESS: -- but we have 18 not discussed ovarian epithelial 19 cells, because I got no changes 20 with talc in ovarian epithelial 21 cells. 22 BY MR. SMITH: 23 Q. Where do the large majority 24 of the ovarian cancers that we discussed</p>	<p>1 A. No one has used fallopian -- 2 normal epithelial cells in any gene 3 profiling assay. We used the most normal 4 cell type that we could get. And that 5 was the ovarian epithelial cell line from 6 Dr. Auersperg. 7 Q. You used immortalized cell 8 in your Shukla study? 9 A. I used contact-inhibited 10 immortalized cells, yes. 11 Q. Okay. And is it appropriate 12 to use immortalized cells in in vitro 13 studies to study -- study cellular 14 reactions? 15 A. It depends on what you're 16 trying to say. If you recall, our 17 emphasis here was to determine in cell 18 lines that are relevant to humans, that 19 is human cell lines, whether significant 20 gene changes were observed with 21 pathogenic mineral findings that were not 22 observed with nonpathogenic mineral 23 fibers. 24 We weren't attempting to do</p>
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<p>1 originate. And that is the serous type. 2 Nearly 90 percent of the epithelial 3 ovarian cancers in the United States, do 4 they originate in the surface of the 5 epithelium of the -- surface area of the 6 ovary or in the fallopian tubes, ma'am? 7 MR. FROST: Objection. 8 THE WITNESS: So we don't 9 know. The majority are thought 10 nowadays to originate in the 11 fallopian tubes. That has no 12 bearing upon our results at all. 13 BY MR. SMITH: 14 Q. I totally agree your results 15 have no bearing on that. 16 MR. FROST: Objection. 17 THE WITNESS: Well, you 18 would like to think so. But the 19 fact remains that we got no 20 changes with talc in ovarian 21 epithelial cells. 22 BY MR. SMITH: 23 Q. Did you use fallopian tube 24 cells in Shukla?</p>	<p>1 transformation. We were attempting to 2 look and see whether minerals at a 3 variety of different comparable surface 4 areas and weight concentrations induced 5 the same responses, and they don't. 6 Talc is inert as is glass 7 beads and titanium dioxide. 8 Q. Inert. What is your 9 definition of inert? 10 A. The same as -- it -- it's 11 uncharged. It's inert in terms of cell 12 reactions. 13 Look at the toxicity data 14 for talc, for example. You have to go 15 extremely high to get a toxic amount. 16 And I would use inert as did IARC 17 repeatedly. 18 Q. So you're saying -- you're 19 saying that talc -- wait. Did you use 20 cosmetic-grade talc or industrial grade 21 talc for Shukla? 22 MR. FROST: Objection. 23 THE WITNESS: You know, I 24 stated that several times. I</p>

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<p>1 think we know the answer. 2 BY MR. SMITH: 3 Q. Okay. You're saying that 4 talc is inert when at 75 micrometers 5 squared per centimeter squared at eight 6 hours, it showed 30 alterations of gene 7 expressions? 8 A. Let's look at our ratio of 9 30 over 3,000 compared to 1 over 3,000. 10 And the 30 -- 11 Q. What -- what comparison are 12 you making that from? 13 MR. FROST: Objection. 14 THE WITNESS: I'm talking 15 about the inert materials that I 16 used. The glass beads -- 17 BY MR. SMITH: 18 Q. Where is that -- where is -- 19 again I'm going to go back to it. 20 If you're going to say, 21 because it's not written in this study 22 anywhere what you just said. 23 What -- what you just said, 24 that talc is inert just like glass beads</p>	<p>1 is the chart in the study that shows me 2 that titanium dioxide and glass beads 3 altered 30 genes at eight hours at 4 75 micrometers squared per centimeter 5 squared in peritoneal mesothelial cells? 6 Show me the chart. 7 MR. FROST: Objection. 8 THE WITNESS: They didn't 9 alter any genes that were elevated 10 above two to three, and the 30 11 that were elevated by talc, which 12 were not seen at a low 13 concentration, were statistically 14 of the same magnitude as what was 15 seen with glass beads and titanium 16 dioxide. 17 And that is expanded upon in 18 the Hillegass paper. 19 BY MR. SMITH: 20 Q. We'll get to that. 21 A. Okay. 22 (Document marked for 23 identification as Exhibit 24 Mossman-39.)</p>
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<p>1 and just like titanium dioxide -- 2 A. Yes. 3 Q. -- and does -- and caused a 4 similar number of gene expression changes 5 as talc so they acted the same, which now 6 I can say they are all inert, even though 7 they changed, altered 30 genes. 8 A. That -- it's insignificant. 9 Q. Show me, show me the chart 10 of where I can go, you know what, 11 Dr. Mossman is right, I can look at this 12 chart over here, it shows gene expression 13 changes, 30 of them. And then I can go 14 over here and look at glass beads and 15 titanium dioxide, and go, wow, they acted 16 the same. Where is that? 17 MR. FROST: Objection. 18 THE WITNESS: Let's look at 19 the fraction of gene changes, and 20 we were looking at thousands of 21 gene changes. 22 So you put 30 -- 23 BY MR. SMITH: 24 Q. Where is the chart? Where</p>	<p>1 BY MR. SMITH: 2 Q. This is Table 6. This is 3 here in your report. Do you recall that? 4 A. Right. 5 Q. Okay. I see talc. I see 6 asbestos -- 7 A. Yeah. 8 Q. -- I see gene changes right 9 here at the higher concentrations. 236 10 of the most potent form of asbestos, 11 crocidolite asbestos, correct? 12 A. That's correct. 13 Q. And you told me that 14 different carcinogens can have varying 15 potencies, correct? 16 A. Different carcinogens? Talc 17 and asbestos are not different 18 carcinogens. 19 Q. In general. Different 20 carcinogens can be of different potency, 21 correct, but they are still carcinogens? 22 MR. FROST: Objection. 23 THE WITNESS: Yeah, I mean 24 that doesn't really make sense.</p>

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<p>1 Everything should have a 2 dose-response and a threshold, and 3 it's going to be different with 4 different materials. 5 BY MR. SMITH: 6 Q. All right. We'll get to 7 that in a minute in Brower, your 8 testimony. 9 A. Okay. 10 Q. All right. Hereafter, look 11 at that, 30 genes altered at -- that 12 should be -- 13 A. That's switched around. 14 You're right. 15 Q. It should be -- that's 16 wrong. It should be eight hours. 17 A. Yeah. 18 Q. Okay. I'm looking right 19 here at fine titanium dioxide and glass 20 beads and low -- and I don't see a high 21 concentration. Why -- where is the high 22 concentration to fine titanium dioxide? 23 MR. FROST: Objection. 24 THE WITNESS: Okay. So if</p>	<p>1 titanium dioxide. 2 Q. Okay. So there is no chart. 3 In fact, there's a chart in 4 your report that shows there are no genes 5 altered by fine titanium dioxide at low 6 concentrations and glass beads at high 7 concentrations, and that talc at high 8 concentrations altered 30 genes, right? 9 A. Yes. But again, I emphasize 10 that we're -- if you put that back on 11 there, we can talk about it. 12 Q. Oh, I'm sorry. 13 A. Okay. So we're looking -- 14 again, the emphasize is on asbestos, and 15 we're looking in mesothelial cells at low 16 and high concentrations at 24 hours to 17 demonstrate a dose-response. We don't -- 18 at low and high concentrations, we get 19 a -- a dose-response. The magnitude is 20 not of the same type. In fact, the 21 changes in the genes, including going up 22 and down, were not of the same type. 23 Q. Ma'am, I asked you earlier. 24 You're the one that went beyond what's</p>
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<p>1 we look at -- 2 BY MR. SMITH: 3 Q. I'm just asking where is it 4 on this chart. 5 A. Okay. At low 6 concentrations, at 24 hours, fine 7 titanium dioxide was run, and the high 8 glass beads were run at eight and 9 24 hours. 10 Q. Ma'am. 11 A. Yeah. 12 Q. Tell me how many genes are 13 altered in this chart by glass beads at 14 high concentrations. 15 A. None. 16 Q. Tell me how many genes are 17 altered by fine titanium dioxide at high 18 concentrations. 19 Was it done? 20 MR. FROST: Objection. 21 BY MR. SMITH: 22 Q. I don't see it. 23 A. It was -- it was done at the 24 low amount and not at the high amount for</p>	<p>1 in -- written down in this report and 2 told me that talc at the high 3 concentrations acted just inert just like 4 fine titanium dioxide and just like glass 5 beads -- 6 A. It -- 7 Q. And now my question to you 8 is -- 9 A. Yes. 10 Q. -- and you said they altered 11 the same amount of genes. And you 12 said -- and I said where is the chart, 13 and you kept answering your question. 14 And I -- so I went and 15 pulled the chart that you have in your 16 report. 17 A. Right. 18 Q. And we can look at how many 19 genes are altered by glass beads at the 20 high concentration, right? 21 What does it say? 22 MR. FROST: Objection. 23 THE WITNESS: Yeah, when -- 24 when one presents microarray data,</p>

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<p style="text-align: right;">Page 394</p> <p>1 you present significant gene</p> <p>2 changes. There's no data here for</p> <p>3 thousands of genes because we</p> <p>4 didn't see any. We're talking</p> <p>5 about bold increases.</p> <p>6 BY MR. SMITH:</p> <p>7 Q. That's what I'm talking</p> <p>8 about.</p> <p>9 A. It's got to be two or</p> <p>10 greater --</p> <p>11 Q. I agree.</p> <p>12 A. So what I'm telling you is</p> <p>13 that with asbestos, we see low, 29, which</p> <p>14 goes up to fourfold higher, eight hours.</p> <p>15 With talc at low, we see an</p> <p>16 insignificant amount compared to the</p> <p>17 other materials we're looking, that does</p> <p>18 not go up like asbestos.</p> <p>19 So we see unique changes to</p> <p>20 asbestos. That's what we are focusing</p> <p>21 on.</p> <p>22 MR. SMITH: That's not my</p> <p>23 question, Doctor. I'm going to</p> <p>24 object to nonresponsiveness.</p>	<p style="text-align: right;">Page 396</p> <p>1 A. There are no genes that are</p> <p>2 increased above twofold levels.</p> <p>3 Q. Thank you.</p> <p>4 A. That's the zero number.</p> <p>5 Q. Does talc have a zero number</p> <p>6 by it at the high concentrations at 24</p> <p>7 hours -- at eight hours?</p> <p>8 A. 30, compared to the total</p> <p>9 number of genes that we looked at, which</p> <p>10 were in the thousands, the ratio of that</p> <p>11 compared to the one ratio with titanium</p> <p>12 dioxide or glass beads was insignificant.</p> <p>13 30 genes means nothing.</p> <p>14 Q. 30 genes means nothing?</p> <p>15 A. That's correct. It's</p> <p>16 insignificant. And that was borne out by</p> <p>17 one set of analyses called ANOVA in the</p> <p>18 Shukla paper and another set of analyses</p> <p>19 called PCA analyses in the Hillegass.</p> <p>20 Q. But you didn't do PCA</p> <p>21 analysis on talc in Hillegass?</p> <p>22 MR. FROST: Objection to</p> <p>23 form.</p> <p>24 THE WITNESS: Yes, we did.</p>
<p style="text-align: right;">Page 395</p> <p>1 BY MR. SMITH:</p> <p>2 Q. My question had to do --</p> <p>3 you're talking -- and stated that talc</p> <p>4 was an inert substance and it did not</p> <p>5 react with cells. And you said it's</p> <p>6 inert just like titanium dioxide and</p> <p>7 glass beads that were controls. And I</p> <p>8 said what is the definition of inert?</p> <p>9 A. Okay. So --</p> <p>10 Q. And you said causes cellular</p> <p>11 responses. And my question to you is,</p> <p>12 show me. I can see where talc at high --</p> <p>13 the higher concentration at eight hours</p> <p>14 altered 30 genes. Show me on this chart</p> <p>15 where glass beads or fine titanium</p> <p>16 dioxide altered any.</p> <p>17 MR. FROST: Objection.</p> <p>18 BY MR. SMITH:</p> <p>19 Q. Can you show it to me?</p> <p>20 MR. FROST: Objection.</p> <p>21 THE WITNESS: It's not on</p> <p>22 this chart.</p> <p>23 BY MR. SMITH:</p> <p>24 Q. In fact, you put zero.</p>	<p style="text-align: right;">Page 397</p> <p>1 It's in the data.</p> <p>2 BY MR. SMITH:</p> <p>3 Q. Okay. We'll get there.</p> <p>4 A. We went through this before.</p> <p>5 Let's look at Figure 1, and the talc data</p> <p>6 is graphed.</p> <p>7 Q. Okay. All right. We'll go</p> <p>8 through it.</p> <p>9 A. Okay.</p> <p>10 Q. You stated earlier in the</p> <p>11 depo that minerals such as asbestos and</p> <p>12 talc react differently to human cells</p> <p>13 depending on the shape, size -- shape,</p> <p>14 size, and crystallinity; is that correct?</p> <p>15 A. Yes.</p> <p>16 Q. And that you admitted that</p> <p>17 shape, size, and crystallinity of</p> <p>18 minerals such as asbestos and talc vary</p> <p>19 from type and grade of talc and different</p> <p>20 types and different mines that they're</p> <p>21 mined from, right?</p> <p>22 A. Yes.</p> <p>23 Q. Okay. And this study did</p> <p>24 not test cosmetic-grade talc, correct?</p>

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<p style="text-align: right;">Page 398</p> <p>1 MR. FROST: Objection.</p> <p>2 THE WITNESS: It tested</p> <p>3 industrial talc.</p> <p>4 BY MR. SMITH:</p> <p>5 Q. It did not test</p> <p>6 cosmetic-grade talc, correct?</p> <p>7 MR. FROST: Objection.</p> <p>8 THE WITNESS: It did not</p> <p>9 look at that directly.</p> <p>10 BY MR. SMITH:</p> <p>11 Q. And it did not -- therefore,</p> <p>12 did not test the type of or the grade of</p> <p>13 talc that's in Baby Powder or Shower to</p> <p>14 Shower, correct?</p> <p>15 MR. FROST: Objection.</p> <p>16 THE WITNESS: The grade of</p> <p>17 talc -- again, you'll have to fill</p> <p>18 me in on what grade means.</p> <p>19 BY MR. SMITH:</p> <p>20 Q. So you don't know that the</p> <p>21 grade of talc that's in Baby Powder or</p> <p>22 Shower to Shower is cosmetic-grade talc?</p> <p>23 A. I'm assuming it is.</p> <p>24 Q. So the study did not examine</p>	<p style="text-align: right;">Page 400</p> <p>1 human fallopian tube cells?</p> <p>2 A. No. Well, let me -- I want</p> <p>3 to qualify that, because I'm not certain</p> <p>4 where these ovarian epithelial cells came</p> <p>5 from. They came from a tissue bank.</p> <p>6 They were normal in terms of -- they grew</p> <p>7 in anchorage-dependent conditions.</p> <p>8 But I don't want to tell you</p> <p>9 what their source is without looking it</p> <p>10 up further.</p> <p>11 Q. In Table 3 of Shukla, the</p> <p>12 genes that were upregulated at</p> <p>13 75 micrometers squared per centimeter</p> <p>14 squared at eight hours, do you know if</p> <p>15 any of those genes have been associated</p> <p>16 with primary peritoneal mesotheliomas?</p> <p>17 MR. FROST: Objection.</p> <p>18 THE WITNESS: The -- I</p> <p>19 don't. They're certainly</p> <p>20 indicative of some of the pathways</p> <p>21 we've followed up on. But we</p> <p>22 haven't isolated these out</p> <p>23 individually to study them.</p> <p>24 BY MR. SMITH:</p>
<p style="text-align: right;">Page 399</p> <p>1 the type or -- the type of talc that is</p> <p>2 in Baby Powder or Shower to Shower, the</p> <p>3 particular grade, correct?</p> <p>4 MR. FROST: Objection.</p> <p>5 THE WITNESS: The source of</p> <p>6 talc was a mining talc.</p> <p>7 BY MR. SMITH:</p> <p>8 Q. And what mine did the talc</p> <p>9 used in the Shukla study come from?</p> <p>10 A. It's something called</p> <p>11 Barrett's Minerals. I don't know where</p> <p>12 the mine is.</p> <p>13 Q. I believe it's in Montana.</p> <p>14 It states in the study.</p> <p>15 Did the study use the talc</p> <p>16 from any of the mines that J&amp;J used for</p> <p>17 its Baby Powder or Shower to Shower</p> <p>18 products, that being from Vermont, Italy,</p> <p>19 Korea, or China?</p> <p>20 MR. FROST: Objection.</p> <p>21 THE WITNESS: No.</p> <p>22 BY MR. SMITH:</p> <p>23 Q. Okay. Have you ever</p> <p>24 performed a study on talc's effect on</p>	<p style="text-align: right;">Page 401</p> <p>1 Q. So you don't know if any of</p> <p>2 these genes that were upregulated in</p> <p>3 Table 3 by talc are actually those genes</p> <p>4 involved in the development of peritoneal</p> <p>5 cancer?</p> <p>6 MR. FROST: Objection.</p> <p>7 THE WITNESS: That's</p> <p>8 correct. I don't know about genes</p> <p>9 that are upregulated in peritoneal</p> <p>10 cancers.</p> <p>11 MR. SMITH: Okay. I'm going</p> <p>12 to attach the next numbered</p> <p>13 exhibit, which would be 40.</p> <p>14 (Document marked for</p> <p>15 identification as Exhibit</p> <p>16 Mossman-40.)</p> <p>17 BY MR. SMITH:</p> <p>18 Q. This is -- the lead author</p> <p>19 is Dragon. Have you ever seen this</p> <p>20 study? It's from 2015.</p> <p>21 A. Yes.</p> <p>22 Q. You have seen this?</p> <p>23 A. I have.</p> <p>24 Q. "Differential Susceptibility</p>

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<p style="text-align: right;">Page 402</p> <p>1 of Human Pleural and Peritoneal 2 Mesothelial Cells to Asbestos Exposure"? 3 A. Yes. 4 Q. It states in the abstract -- 5 actually this is from Vermont College 6 here, right, College of Medicine? 7 A. Yeah. Dr. Shukla is the 8 senior author. 9 Q. That's correct. And the 10 abstract, "Malignant mesothelioma, or MM, 11 is an aggressive cancer of mesothelial 12 cells of the pleural and peritoneal 13 cavities. In 85 percent of cases both 14 pleural and peritoneal malignant 15 mesothelioma is caused by asbestos 16 exposure. Although both are 17 asbestos-induced cancers, the incidence 18 of pleural malignant mesothelioma is 19 significantly higher at 85 percent than 20 peritoneal malignant mesothelioma at 21 15 percent." 22 And down at the bottom it 23 says, "Our results are consistent with 24 the hypothesis that differences in</p>	<p style="text-align: right;">Page 404</p> <p>1 mesothelioma. 2 Do you see that, the fold 3 changes? 4 A. These aren't mesothelioma 5 cells. These are two normal cell lines 6 that are normal pleural mesothelial cells 7 and a cell line including one we used in 8 our study, that were peritoneal. 9 Q. Correct. 10 A. So these are not tumors. 11 You can't say anything about -- 12 Q. That's not what I'm -- I 13 didn't mention tumor. You're the one 14 that brought up tumor. I did not say 15 that, did I? 16 A. No, you didn't, but you said 17 mesothelioma cells. 18 Q. Well, we see that IL-8, 19 CXCL2, CXCL3, IL-6, ATF3 were all 20 upregulated in pleural mesothelial cells 21 and in peritoneal mesothelial cells. 22 Do you see that? 23 A. Yes. By asbestos. 24 Q. Okay. And were those some</p>
<p style="text-align: right;">Page 403</p> <p>1 incidences of pleural and peritoneal 2 malignant mesothelioma upon exposure to 3 asbestos are the result of differences in 4 mesothelial cell physiology that lead to 5 differences in the inflammatory response 6 which leads to cancer." 7 Do you see that? 8 A. I do. 9 Q. Do you agree with that? 10 MR. FROST: Objection. 11 THE WITNESS: I do with 12 regard to asbestos. 13 BY MR. SMITH: 14 Q. Okay. And if you flip to 15 Page 24. It's a chart. If you look at 16 it, Figure A is transcripts known to be 17 involved with malignant mesothelioma that 18 were significantly differential -- 19 differentially expressed in all cell 20 lines. 21 But if you look at IL-8 22 IL-6, ATF3, ATF3, the CXCL2, CXCL3, those 23 were all altered in malignant 24 mesothelioma and in peritoneal</p>	<p style="text-align: right;">Page 405</p> <p>1 of the same cell lines -- excuse me. 2 Were those some of the same genes, IL-8, 3 CXCL2, CXCL3, IL-6 and ATF3 that were 4 upregulated in peritoneal mesothelial 5 cells at the concentrations of eight 6 hours of talc in your study in Shukla? 7 MR. FROST: Objection. 8 THE WITNESS: Some of them, 9 certainly the ATF3 was. 10 BY MR. SMITH: 11 Q. IL-8? 12 A. IL-8, which could have many 13 functions. 14 Q. CXCL2 and CXCL3, correct? 15 A. I'd have to go back and 16 look, but they're chemokines. I believe 17 one of them might have been upregulated 18 by talc. 19 Q. IL-6? 20 A. Yeah. And this all makes 21 sense, because we know that talc induces 22 acute inflammation and antiinflammation 23 at -- by ATF3 is -- is a -- certainly a 24 protective response of the cells.</p>

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<p>1 Q. And that was -- and the 2 same -- and pleural mesothelial cells 3 were upregulated, those same genes were 4 upregulated by crocidolite asbestos that 5 we know, you admit, causes mesothelioma, 6 correct? 7 A. Are you suggesting that 8 because a gene goes up it's associated 9 with mesothelioma? 10 Q. No, I'm just saying, would 11 you agree with me that this chart shows 12 and tests crocidolite asbestos and shows 13 gene changes in pleural mesothelial 14 cells? 15 A. It shows gene changes in 16 pleural and peritoneal mesothelial 17 cells -- 18 Q. And my question -- 19 A. Yeah. 20 Q. -- my question is, would you 21 agree with me that crocidolite asbestos 22 causes malignant mesothelioma? 23 MR. FROST: Objection. 24 THE WITNESS: Yes. But</p>	<p>1 you produced documents. Do you recall 2 that? 3 A. I do. 4 Q. And -- and I'm going to 5 attach that as an Exhibit 41. 6 (Document marked for 7 identification as Exhibit 8 Mossman-41.) 9 BY MR. SMITH: 10 Q. And just show it to you. Do 11 you recall this? Affidavit of Brooke 12 Mossman you provided to me? 13 A. Yes. 14 Q. Okay. And -- and I'll show 15 you your signature at the back. 16 A. Okay. 17 Q. And that's your signature 18 you provided to me? 19 A. Yes. 20 Q. Okay. I'm going to attach 21 that as Exhibit 41. 22 And you produced some 23 documents to me. Some of -- some of 24 them -- and there were a lot -- of drafts</p>
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<p>1 that's not what we're -- we're 2 looking at here. 3 BY MR. SMITH: 4 Q. Okay. That's not what I'm 5 saying. I'm just showing, on this chart, 6 the different gene changes that by a 7 known substance to cause malignant 8 mesothelioma, right? 9 And some of the genes that 10 were changed are IL-8, CXCL2, CXCL3, 11 IL-6, ATF3. And those were the same 12 genes that were upregulated by talc at 13 the higher concentration at eight hours 14 in your Shukla paper, right? 15 MR. FROST: Objection. 16 THE WITNESS: Some of them 17 were. I would say half of the 18 genes that were significant, the 19 IL-8, the ATF3, I believe one of 20 the CXCL2s or 3. So some of them 21 were common. Other ones were not. 22 BY MR. SMITH: 23 Q. Okay. You provided an 24 affidavit to me in the Brower case, and</p>	<p>1 of the Shukla paper. Do you recall that? 2 A. Yeah. 3 Q. There were like a bunch of 4 them. 5 A. It was -- it was the same 6 paper xeroxed many times. Yes. 7 Q. And so this was just earlier 8 drafts or the drafts that eventually 9 became the Shukla paper that we just went 10 over, correct? 11 A. Yes. 12 (Document marked for 13 identification as Exhibit 14 Mossman-42.) 15 BY MR. SMITH: 16 Q. Okay. I'm going to attach 17 this as Exhibit 42. And it's entitled, 18 "Alterations in Gene Expression in Human 19 Mesothelial Cells Correlate With Mineral 20 Pathogenicity." 21 It has Shukla at the 22 beginning and looks almost exactly like 23 the study that we attached as Exhibit 34, 24 that was a peer-reviewed published</p>

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<p>1 publication, correct?</p> <p>2 A. Yes.</p> <p>3 Q. Okay. And if you go to</p> <p>4 Page 3, and look at the first large</p> <p>5 paragraph in the last sentence.</p> <p>6 A. Mm-hmm.</p> <p>7 Q. "Moreover, the early</p> <p>8 molecular events leading to injury by</p> <p>9 asbestos fibers and other pathogenic or</p> <p>10 innocuous particulates in human cells</p> <p>11 that may be targets for the development</p> <p>12 of disease remain enigmatic."</p> <p>13 And that's the reason you</p> <p>14 performed this study to look at those</p> <p>15 changes, right?</p> <p>16 A. We were interested in gene</p> <p>17 profiling, yes, that's correct.</p> <p>18 Q. Okay. And if you go to the</p> <p>19 second paragraph, and you go just past</p> <p>20 Number 6. It's one, two, three, four,</p> <p>21 five, six lines down.</p> <p>22 "This cell type is not</p> <p>23 implicated in asbestos-induced diseases,</p> <p>24 but is occasionally linked to the</p>	<p>1 MR. FROST: Objection.</p> <p>2 THE WITNESS: I believe it</p> <p>3 is in the Hillegass paper. And I</p> <p>4 seem to remember when I looked</p> <p>5 over this correspondence that this</p> <p>6 was a comment that one of the</p> <p>7 reviewers questioned, and he put</p> <p>8 in additional references.</p> <p>9 BY MR. SMITH:</p> <p>10 Q. I thought we might go to the</p> <p>11 reviewer comments because we have it</p> <p>12 attached as Exhibit 36.</p> <p>13 A. Yeah. I remember that.</p> <p>14 Q. Show me in the reviewer</p> <p>15 comments where they say take that out.</p> <p>16 A. The Hillegass paper. They</p> <p>17 asked us --</p> <p>18 Q. No, ma'am. Ma'am.</p> <p>19 A. No.</p> <p>20 Q. This is Shukla.</p> <p>21 A. Yeah.</p> <p>22 Q. This is the Shukla paper.</p> <p>23 This is the draft of the Shukla paper.</p> <p>24 And that statement is in a draft of the</p>
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<p>1 inflammation and development of ovarian</p> <p>2 cancer after use of talcum powder in the</p> <p>3 pelvic region, albeit highly</p> <p>4 controversial."</p> <p>5 Why didn't that statement</p> <p>6 make it into the final?</p> <p>7 MR. FROST: Objection.</p> <p>8 THE WITNESS: This cell type</p> <p>9 is not implicated...</p> <p>10 BY MR. SMITH:</p> <p>11 Q. Can you tell me why that</p> <p>12 statement, and I went through all of</p> <p>13 them, and that's the only statement,</p> <p>14 otherwise they read just exactly alike.</p> <p>15 "This cell type is not implicated in</p> <p>16 asbestos-induced diseases, but is</p> <p>17 occasionally linked to inflammation and</p> <p>18 the development of ovarian cancer after</p> <p>19 use of talcum powder in the pelvic</p> <p>20 region, albeit highly controversial."</p> <p>21 I want to know why that</p> <p>22 statement was taken out of the drafts and</p> <p>23 not in the final peer-reviewed</p> <p>24 publication.</p>	<p>1 Shukla paper that you provided me per the</p> <p>2 affidavit that we just went over in</p> <p>3 Exhibit 41.</p> <p>4 And I want you to show me in</p> <p>5 the Shukla paper that we just went over,</p> <p>6 it's peer reviewed, Exhibit Number 34 --</p> <p>7 A. Yeah.</p> <p>8 Q. -- where that statement is</p> <p>9 in that study that's in the draft that</p> <p>10 you provided to me.</p> <p>11 MR. FROST: Objection.</p> <p>12 THE WITNESS: Okay. So I'm</p> <p>13 looking at the Shukla paper, and</p> <p>14 that statement was Merritt in 2009</p> <p>15 and it is in this. So...</p> <p>16 BY MR. SMITH:</p> <p>17 Q. Where is it?</p> <p>18 A. All right. Let me just</p> <p>19 look. It's Reference Number 7?</p> <p>20 It says -- although I'm</p> <p>21 admitting that you looked this -- looked</p> <p>22 this over very well. It says, "This cell</p> <p>23 type is not implicated in</p> <p>24 asbestos-induced diseases but is</p>

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<p style="text-align: right;">Page 414</p> <p>1 occasionally linked to inflammation and</p> <p>2 the development of ovarian cancer after</p> <p>3 use of talcum powder in the pelvic</p> <p>4 region, although such links are highly</p> <p>5 controversial."</p> <p>6 Q. Where is it?</p> <p>7 A. It's in the final</p> <p>8 publication, exactly where I --</p> <p>9 Q. I know. Point me to it. I</p> <p>10 just missed it. Where is it?</p> <p>11 A. Yeah, I guess you did.</p> <p>12 Q. I guess I did. I'm -- I am</p> <p>13 mortal. I apologize.</p> <p>14 Where is it?</p> <p>15 A. Here you go.</p> <p>16 Q. Can you show me? Can you</p> <p>17 tell me where the --</p> <p>18 A. It's exactly where it was in</p> <p>19 the draft, yeah.</p> <p>20 MR. FROST: If you look at</p> <p>21 Page 1, right-hand column. It's</p> <p>22 the first full paragraph, last</p> <p>23 sentence.</p> <p>24 BY MR. SMITH:</p>	<p style="text-align: right;">Page 416</p> <p>1 MR. FROST: Take a short</p> <p>2 break.</p> <p>3 MR. SMITH: Sure. We can</p> <p>4 take a quick break.</p> <p>5 THE VIDEOGRAPHER: Going off</p> <p>6 the record. The time is 4:23.</p> <p>7 (Short break.)</p> <p>8 THE VIDEOGRAPHER: We are</p> <p>9 going back on record. Beginning</p> <p>10 of Media File Number 5. The time</p> <p>11 is 4:38.</p> <p>12 BY MR. SMITH:</p> <p>13 Q. Okay. So in Exhibit 39,</p> <p>14 which is a chart in your study, I need to</p> <p>15 correct --</p> <p>16 A. Yes.</p> <p>17 Q. I need to switch 24 to</p> <p>18 eight --</p> <p>19 A. Right.</p> <p>20 Q. -- and eight to 24, right?</p> <p>21 A. Yes. That's correct.</p> <p>22 Q. And I made those changes.</p> <p>23 Okay. And then over here,</p> <p>24 I've got a question in -- you have talc</p>
<p style="text-align: right;">Page 415</p> <p>1 Q. I missed it. I stand</p> <p>2 corrected.</p> <p>3 A. Wow.</p> <p>4 Q. I highlighted it right</p> <p>5 before it. Thank you.</p> <p>6 A. You're welcome.</p> <p>7 Q. Do you agree with that</p> <p>8 statement, now that it's -- we've</p> <p>9 established that it's in your study?</p> <p>10 A. I agree that it's highly</p> <p>11 controversial still.</p> <p>12 Q. Do you agree that it's been</p> <p>13 occasionally linked to inflammation in</p> <p>14 the development of ovarian cancer use</p> <p>15 after the use of talcum powder in the</p> <p>16 pelvic region?</p> <p>17 A. I believed in 2009, we</p> <p>18 referenced or we looked at the Ness and</p> <p>19 Cottreau, which was a hypothesis paper</p> <p>20 and it is still a hypothesis that the</p> <p>21 scientific data does not support.</p> <p>22 Q. Okay. Let's talk about --</p> <p>23 MR. SMITH: Are we okay? Or</p> <p>24 can we keep going?</p>	<p style="text-align: right;">Page 417</p> <p>1 at low concentrations of ovarian</p> <p>2 epithelial cells, zero.</p> <p>3 Do you see that?</p> <p>4 A. It should be -- it should be</p> <p>5 high because we only added talc to the</p> <p>6 ovarian epithelial cells at high</p> <p>7 concentrations. So these -- they're the</p> <p>8 right word, but they need to come down a</p> <p>9 little bit.</p> <p>10 Q. I'm with you.</p> <p>11 A. See.</p> <p>12 Q. So this should be -- right</p> <p>13 here this should be zero right here?</p> <p>14 A. Right.</p> <p>15 Q. And that should be -- that</p> <p>16 mark right there is for low</p> <p>17 concentration?</p> <p>18 A. Right. Right. Right.</p> <p>19 So in this case, yes.</p> <p>20 Q. All right. If you look at</p> <p>21 your paper --</p> <p>22 A. Yeah.</p> <p>23 Q. -- and you go to --</p> <p>24 A. Which one? The Shukla?</p>

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<p style="text-align: right;">Page 418</p> <p>1 Q. Shukla. 2 A. Okay. 3 MR. MIZGALA: I think it was 4 right the way it was. 5 THE WITNESS: High had no 6 results. 7 MR. SMITH: That's right. 8 BY MR. SMITH: 9 Q. All right. These are the 10 epithelial -- ovarian epithelial cells, 11 right? 12 A. Yes. 13 Q. Okay. And at 24 hours you 14 have zero at high concentrations, right? 15 Cell -- gene changes, right? 16 A. Yes. 17 Q. Okay. If you look at Page 5 18 of 10. 19 A. Yes. 20 Q. And it says, "At 21 24 hours" -- down at the bottom under 22 "IOSE ovarian epithelial cells exhibit 23 few gene expression changes," it says, 24 "At 24 hours, high concentrations of</p>	<p style="text-align: right;">Page 420</p> <p>1 A. This is the -- 2 MR. FROST: Objection. 3 THE WITNESS: -- gene -- 4 you're talking about the toxicity 5 data here. We did -- and I 6 believe it's stated in this paper. 7 We did a range of concentrations 8 with the talc up to 20. And I 9 think we make the statement that 10 in no cases was there toxicity to 11 the ovarian epithelial cells. So 12 it's here somewhere. 13 BY MR. SMITH: 14 Q. Well, my question is also, I 15 didn't think you tested talc at high 16 concentrations. 17 A. We only did that in the 18 ovarian epithelial cells, because of -- 19 we, in all of these, we had done 20 preliminary studies, and our original 21 ones indicated that we had no toxicity 22 and no effect. So we did the whole 23 experiment for microarrays at the high 24 concentration.</p>
<p style="text-align: right;">Page 419</p> <p>1 asbestos caused less than fourfold 2 increases in expression of only 16 genes 3 and decreased" -- hold on. Am I in the 4 right spot? No, I'm not. 5 Let's go back to 4 of 10. 6 I'm sorry. 7 A. Okay. 8 Q. "Asbestos fibers at high 9 concentrations are toxic to TP9/TERT-1 10 mesothelial cells and less so to ovarian 11 epithelial cells in contrast to particle 12 preparations." 13 It talks about, "Non-fibrous 14 talc at 75 micrometers squared per 15 centimeter squared was nontoxic, and 16 significant increases in toxicity were 17 only achieved with addition of talc at 18 greater than threefold concentrations in 19 LP9/TERT-1 cells (Figure 2A), but not in 20 IOSE cells (data not shown)." 21 A. Right. 22 Q. Okay. Is that -- data 23 not -- how -- where is this data to be 24 able to put zero down here? I don't --</p>	<p style="text-align: right;">Page 421</p> <p>1 Q. Where is that data that 2 shows that? 3 A. Okay. It's probably in here 4 somewhere. 5 Q. And data -- 6 A. Here we go. 7 Q. Data not shown or 8 referenced, where can I get that data? 9 A. I believe some of it might 10 have been in supplementary data in this 11 journal. 12 Q. Can you give me a 13 supplemental journal where that -- 14 A. Wait. Let me just make sure 15 then. Figure 2D. Okay. So, in terms of 16 the toxicity data for talc, it is in 17 Figure 2D, and that's the ovarian 18 epithelial cells. So there is data 19 presented on the cytotoxicity. 20 Q. Well, hold on a second, 21 because Table 6 it says -- in your -- 22 right here on Exhibit 39. Table 6, "Talc 23 does not cause altered gene expression in 24 human mesothelial or ovarian epithelial</p>

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<p>1 cells."</p> <p>2 We're not talking about</p> <p>3 toxicity. We're talking about gene</p> <p>4 expression changes.</p> <p>5 A. Right.</p> <p>6 Q. And you're writing zero down</p> <p>7 right here that you tested talc at high</p> <p>8 concentrations and got zero gene</p> <p>9 expression changes.</p> <p>10 My question is, where is</p> <p>11 that?</p> <p>12 A. Not in -- it says -- okay.</p> <p>13 (Reading to herself.)</p> <p>14 Okay. So if it didn't have</p> <p>15 any significant gene changes, like for</p> <p>16 the other materials, it wouldn't have</p> <p>17 been presented, because there was no</p> <p>18 significant increase in any of the genes.</p> <p>19 Q. Well, you have zero here.</p> <p>20 Where is that? Where does it show that</p> <p>21 there are no -- no changes? Where does</p> <p>22 it state that?</p> <p>23 A. It's stated here. Hold on.</p> <p>24 I think we've got it with the asbestos.</p>	<p>1 were just discussing, and it says data</p> <p>2 not shown.</p> <p>3 A. Right. No significant gene</p> <p>4 upregulation or downregulation in</p> <p>5 response to lower concentrations of</p> <p>6 asbestos. So no significant changes,</p> <p>7 data not shown. At high concentrations</p> <p>8 are what is expressed in Table 4.</p> <p>9 Q. Where are you reading that?</p> <p>10 A. I'm reading this on 5 of 10</p> <p>11 under IOSE ovarian epithelial cells.</p> <p>12 Q. It says, "Data not shown,"</p> <p>13 correct?</p> <p>14 A. That's correct.</p> <p>15 Q. Where can I get that data?</p> <p>16 A. It could be supplemental or</p> <p>17 it may not have been presented at all.</p> <p>18 Q. Would I have -- would there</p> <p>19 be any notes or lab notes or anything, or</p> <p>20 where -- I mean, I haven't seen an</p> <p>21 updated study of where that -- where you</p> <p>22 get zero here, besides a statement. I</p> <p>23 don't see like any testing or tables.</p> <p>24 MR. FROST: Objection.</p>
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<p>1 Okay. Let me just see if it's in the --</p> <p>2 Okay. So, yeah. So this is important to</p> <p>3 look at, because in Table 4 at the high</p> <p>4 concentrations, you see only one number</p> <p>5 at the top, and the 2s are not</p> <p>6 significantly elevated.</p> <p>7 So the data is just shown at</p> <p>8 the high concentrations of materials. At</p> <p>9 the low concentrations there were no gene</p> <p>10 changes.</p> <p>11 Q. I understand that. But</p> <p>12 where -- I see the genes upregulated by</p> <p>13 crocidolite asbestos and IOSE human</p> <p>14 ovarian cells.</p> <p>15 A. Yes.</p> <p>16 Q. I do not a -- I do not see a</p> <p>17 table or a sentence about zero being</p> <p>18 found for talc.</p> <p>19 A. It's stated.</p> <p>20 Q. Where?</p> <p>21 A. In the results. Let's look</p> <p>22 where we describe the IO cells.</p> <p>23 All right.</p> <p>24 Q. I thought that's what we</p>	<p>1 THE WITNESS: I think it's</p> <p>2 the same thing that I explained to</p> <p>3 you before, is that we got no</p> <p>4 significant gene changes looking</p> <p>5 at thousands of genes, and that</p> <p>6 you don't -- you present in these</p> <p>7 findings what you did find, which</p> <p>8 are what you see in all these</p> <p>9 figures.</p> <p>10 So for any gene expression</p> <p>11 data, you're not going to see</p> <p>12 numbers or negative numbers for</p> <p>13 5,000 or some odd genes. It's --</p> <p>14 you don't express it like that.</p> <p>15 BY MR. SMITH:</p> <p>16 Q. So there was data. It just</p> <p>17 wasn't included in this study.</p> <p>18 A. No. It was included in the</p> <p>19 statistical analyses, but it was</p> <p>20 insignificant; therefore, it was not</p> <p>21 graphed, because the numbers were at the</p> <p>22 ordinate of each graph.</p> <p>23 Q. I want to talk about the</p> <p>24 Hillegass study.</p>

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<p style="text-align: right;">Page 426</p> <p>1 A. Okay.</p> <p>2 MS. O'DELL: Excuse me for a</p> <p>3 moment. We Request that data that</p> <p>4 Dr. Mossman has just testified to,</p> <p>5 including the raw data, any</p> <p>6 statistical analyses and outputs</p> <p>7 of where the affected data has</p> <p>8 been noted.</p> <p>9 THE WITNESS: This paper was</p> <p>10 15 years ago. So there's not</p> <p>11 going to be any data. We did the</p> <p>12 literature search to try and find</p> <p>13 it.</p> <p>14 MS. O'DELL: The -- there's</p> <p>15 data that's published in the table</p> <p>16 in her report that's not reflected</p> <p>17 in the peer-reviewed publication,</p> <p>18 and we want to know what the</p> <p>19 underlying basis is for that data.</p> <p>20 So that's the question.</p> <p>21 MR. FROST: We'll take it</p> <p>22 under advisement. Just send a</p> <p>23 letter, take it under advisement.</p> <p>24 Or an e-mail.</p>	<p style="text-align: right;">Page 428</p> <p>1 was pathogenic, correct?</p> <p>2 A. Yes.</p> <p>3 Q. And since talc was not</p> <p>4 subject to this test, we don't know what</p> <p>5 cytokines would have been released with</p> <p>6 exposure to talc and its relevance to</p> <p>7 talc's ability to cause disease from this</p> <p>8 study, correct?</p> <p>9 MR. FROST: Objection.</p> <p>10 THE WITNESS: Right. The</p> <p>11 levels of gene expression by talc</p> <p>12 were so small that we would not</p> <p>13 have expected an increase in terms</p> <p>14 of proteins.</p> <p>15 BY MR. SMITH:</p> <p>16 Q. That -- that wasn't my</p> <p>17 question.</p> <p>18 My question was, since</p> <p>19 talc --</p> <p>20 MR. SMITH: And I object to</p> <p>21 nonresponsiveness.</p> <p>22 BY MR. SMITH:</p> <p>23 Q. Since talc was not subjected</p> <p>24 to this test, we do not know what</p>
<p style="text-align: right;">Page 427</p> <p>1 BY MR. SMITH:</p> <p>2 Q. Let's move to the Hillegass</p> <p>3 study. And that's Exhibit 35. What type</p> <p>4 of asbestos did you look at in this</p> <p>5 study?</p> <p>6 A. It's crocidolite.</p> <p>7 Q. And is crocidolite one of</p> <p>8 the asbestos types that is found in Baby</p> <p>9 Powder or Shower to Shower that we</p> <p>10 discussed earlier?</p> <p>11 A. Not to my knowledge.</p> <p>12 Q. And you told me earlier that</p> <p>13 different types of asbestos affect human</p> <p>14 cells in different ways, correct?</p> <p>15 A. Yes. Our studies have been</p> <p>16 with chrysotile and crocidolite asbestos,</p> <p>17 and amosite, which falls into the same</p> <p>18 category as crocidolite in terms of</p> <p>19 results on cells.</p> <p>20 Q. Hillegass study involved</p> <p>21 gene profiling and proteomics, bioplex</p> <p>22 proteins, cytokines released from</p> <p>23 peritoneal mesothelial cells exposed to</p> <p>24 asbestos to determine if asbestos was --</p>	<p style="text-align: right;">Page 429</p> <p>1 cytokines would have been released with</p> <p>2 exposure to talc and its relevance to</p> <p>3 talc's ability to cause disease from this</p> <p>4 study, correct?</p> <p>5 MR. FROST: Objection.</p> <p>6 THE WITNESS: Again, we</p> <p>7 didn't look at that because the</p> <p>8 results were reversible and not of</p> <p>9 a magnitude that one would expect</p> <p>10 protein to be increased.</p> <p>11 BY MR. SMITH:</p> <p>12 Q. Okay. I asked you this</p> <p>13 question in Brower, do you recall that?</p> <p>14 MR. FROST: Objection.</p> <p>15 THE WITNESS: No.</p> <p>16 BY MR. SMITH:</p> <p>17 Q. Okay. Look at Page 195 of</p> <p>18 your testimony in Brower. 194 and 195.</p> <p>19 A. Okay. 194 and 195?</p> <p>20 Q. Correct.</p> <p>21 A. Okay.</p> <p>22 Q. And I'm going to start on</p> <p>23 Line --</p> <p>24 A. Okay.</p>

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<p style="text-align: right;">Page 430</p> <p>1 Q. -- 10 -- or I'm going to 2 start on Line 8. 3 Can we go -- "Question: Can 4 we go back to the Hillegass study? 5 "Answer: Sure. 6 "Question: There were 7 additional tests done on asbestos that 8 were not done for talc in the study; is 9 that correct? 10 "Answer: As I remember it, 11 yes. 12 "Okay. What additional 13 tests were done on asbestos that were not 14 performed on talc? 15 "Answer: We used what was 16 called a bioplex assay to examine 17 additional -- what are called 18 cytokines -- that were released from the 19 LP9 cell line after exposure to 20 crocidolite. 21 "Question: So given the 22 fact that you didn't do the similar test 23 on talc or the peritoneal mesothelial 24 cells, you can't tell me what additional</p>	<p style="text-align: right;">Page 432</p> <p>1 from talc, correct? 2 MR. FROST: Objection. 3 THE WITNESS: I'm sorry. 4 I'm -- 5 MR. FROST: Do you want to 6 see the question or have it 7 read -- 8 THE WITNESS: Yeah. In your 9 studies, that being -- 10 BY MR. SMITH: 11 Q. In your studies you were 12 able to get additional information about 13 whether asbestos was carcinogenic to 14 cells, thought to be the origin of 15 ovarian cancer, that you failed to obtain 16 from talc, correct? 17 A. We weren't looking at 18 additional -- we weren't looking at 19 whether asbestos was carcinogenic to 20 cells in these studies. We were trying 21 to determine whether the gene profiling 22 changes that we saw in the Shukla studies 23 were reflected by increased release of 24 proteins from the cells.</p>
<p style="text-align: right;">Page 431</p> <p>1 cytokines would have been released in 2 that regard?" 3 And there was an objection. 4 "The witness: Yeah. I 5 can't" -- 6 "Answer: I can't tell you 7 the additional cytokines that were 8 released by talc because we didn't look 9 at that." 10 Is that your answer? Is 11 that correct? 12 MR. FROST: Objection. 13 THE WITNESS: Yes. If it 14 had been indicated that there were 15 elevations like asbestos, we would 16 have done the studies with talc, 17 but that was not the case. 18 BY MR. SMITH: 19 Q. In your study -- studies, 20 and that being Hillegass, you were able 21 to get additional information about 22 whether asbestos was carcinogenic to 23 cells, thought to be the origin of 24 ovarian cancer, that you failed to obtain</p>	<p style="text-align: right;">Page 433</p> <p>1 Q. Go to Page 196 of the Brower 2 testimony. 3 A. Mm-hmm. Okay. 196? 4 Q. Yes, ma'am. 5 A. Okay. 6 Q. Line 3. 7 A. Mm-hmm. 8 Q. "Question: So you were able 9 to get additional information about 10 whether or not crocidolite asbestos was 11 carcinogenic or not compared to 12 neomesothelial cells by doing these 13 additional studies? 14 "Answer: In general, yes." 15 Is that your answer? Is 16 that correct? 17 Is that statement correct 18 that you stated in Brower? 19 A. We were getting additional 20 information. Certainly from the study, 21 but the way your sentence is worded, your 22 question is worded, about whether or not 23 crocidolite asbestos was carcinogenic or 24 not, was not a focus of these studies</p>

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<p style="text-align: right;">Page 434</p> <p>1 whereby -- or would be gained by 2 information on these additional studies. 3 MR. SMITH: I'm going to 4 object as nonresponsive. 5 BY MR. SMITH: 6 Q. I'm going to read the 7 question and answer again. 8 "So you weren't able to get 9 additional information about whether or 10 not crocidolite asbestos was carcinogenic 11 or not compared to neomesothelial cells 12 by doing these additional studies?" And 13 we're talking about Hillegass. And your 14 answer was: "In general, yes." 15 Is that true, is that a true 16 statement? 17 MR. FROST: Objection. 18 THE WITNESS: Yeah. Let me 19 emphasize again that the 20 additional information we were 21 getting was whether genes that we 22 saw in Shukla resulted in protein 23 secretion by mesothelial cells 24 after exposure to crocidolite</p>	<p style="text-align: right;">Page 436</p> <p>1 Q. I think we attached it as an 2 exhibit to the deposition. 3 A. All right. Mm-hmm. If I 4 can find it in the pile here. Okay. 5 Q. When did you draft your 6 report and reach your conclusions? It's 7 dated February 25th, 2019. I think you 8 said some time in December or January 9 2018, 2019. Would that be correct? 10 A. Sometime in that realm, yes. 11 Q. What methodology did you use 12 in arriving at your opinions in this 13 case? 14 A. I used the same methodology 15 that I would have in our researching any 16 scientific review. 17 Q. And what is that? 18 A. Search of the peer-reviewed 19 literature on the topic. I was also 20 asked to comment on two expert reports. 21 And in that case, I looked at each 22 statement, each reference, and then I did 23 a literature review of my own to pull up 24 other possibly relevant papers.</p>
<p style="text-align: right;">Page 435</p> <p>1 asbestos. 2 This is a long leap in terms 3 of determining whether or not 4 crocidolite asbestos is 5 carcinogenic to peritoneal 6 mesothelial cells. We weren't 7 looking at that in these studies. 8 BY MR. SMITH: 9 Q. Can I rely on your answer in 10 the Brower case? 11 MR. FROST: Objection. 12 THE WITNESS: I'm qualifying 13 it. I say in general. 14 Again, I'm trying to make it 15 clear that we were looking at 16 proteins that were released from 17 these cells. Are there links 18 between these and cancer-causing 19 effects? Not necessarily. And 20 that's my answer. 21 BY MR. SMITH: 22 Q. All right. I would like to 23 talk to you about your report. 24 A. Okay.</p>	<p style="text-align: right;">Page 437</p> <p>1 So my methodology was the 2 same as I would have done in this case in 3 review of scientific papers submitted by 4 others to journals. 5 I'm missing my report here. 6 Q. Can you -- how did you 7 compile the literature or compile the 8 literature search that you did in this 9 area? 10 A. I did a PubMed search. 11 Q. Of what? 12 A. I looked at asbestos and 13 ovarian cancer. I put in talc and 14 ovarian cancer. I looked at all the 15 references that were cited by 16 Drs. Zelikoff and Saed and read those 17 papers, and then I looked at statements 18 in those papers and how they were 19 referenced. So I had an additional 20 volume of information. 21 Q. You said that you used the 22 methodology that you used in your 23 peer-reviewed literature; is that 24 correct?</p>

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<p style="text-align: right;">Page 438</p> <p>1 A. I used the peer-review 2 process in order to compile the work. I 3 cited work that I'd done in peer-reviewed 4 journals. And I also -- thank you. 5 And I also looked at the 6 IARC -- two reports, which are not peer 7 reviewed. 8 Q. The IARC monograph is not 9 peer-reviewed? 10 A. No, it's not. It's not in a 11 peer-reviewed database. 12 Q. Are your opinions in this 13 case peer reviewed? Is your report peer 14 reviewed? 15 A. My report is based upon my 16 review of peer-reviewed data. 17 Q. Is your report in this case 18 a peer-reviewed study? 19 A. It's not. It's an opinion, 20 or set of opinions. 21 Q. In your opinion -- and we'll 22 look at it in a minute. I don't see 23 anywhere in your -- and I could be wrong, 24 like I missed something before earlier,</p>	<p style="text-align: right;">Page 440</p> <p>1 Q. Do the Shukla and Hillegass 2 studies play a major role in the basis of 3 your opinions in this case? 4 MR. FROST: Objection. 5 THE WITNESS: They add basis 6 to the studies that I reviewed. 7 So I would include these as well 8 as the animal studies and the 9 epidemiology and other mechanistic 10 studies as related to my final 11 opinions. 12 BY MR. SMITH: 13 Q. Did you examine all the 14 available data on cells responsible for 15 ovarian cancer and its interaction with 16 cosmetic-grade talc, that being the type 17 that's in Baby Powder and Shower to 18 Shower? 19 A. Could you state that again. 20 I'm sorry. 21 Q. Did you explain all the 22 available data on cells responsible for 23 ovarian cancer and its interaction with 24 cosmetic-grade talc, that being the type</p>
<p style="text-align: right;">Page 439</p> <p>1 but I didn't see anywhere in your report 2 where you state that you do not believe 3 that talc -- there's no statement that I 4 recall that you do not hold the opinion 5 that talc does not cause ovarian cancer. 6 MR. FROST: Objection. 7 BY MR. SMITH: 8 Q. Do you recall that being 9 stated in your report? 10 A. I don't. But I'd have to go 11 through it. 12 Q. Are all your opinions in 13 this case contained in that report? 14 A. Yes. I'm wondering whether 15 it's in the summary or the end of the 16 reports. 17 Q. We'll go through your bullet 18 points -- 19 A. Okay. 20 Q. -- and we'll come back to 21 that. 22 A. Okay. It might be in there. 23 I just don't know where it would be 24 stated in terms of that precise sentence.</p>	<p style="text-align: right;">Page 441</p> <p>1 that's in Baby Powder and Shower to 2 Shower? 3 A. If I pulled the information 4 up on PubMed, if there was research out 5 there, I would have pulled it up. I 6 don't recall any studies in vitro that 7 focused on cosmetic talc with the 8 exception of Dr. Saed's. 9 Q. Did you examine all the 10 available data on cells responsible for 11 ovarian cancer and its interaction of the 12 types of asbestos found in Baby Powder 13 and Shower to Shower? 14 A. That's not a simple yes or 15 no question. Again, if there were papers 16 that were in the peer-reviewed scientific 17 literature on talcs, I would have gotten 18 those. Whether they were specifically 19 regarding cosmetic talcs or industrial 20 talcs or pharmaceutical-grade talcs, that 21 would have been in the papers themselves. 22 Q. Let's go to your report. 23 A. Okay. 24 Q. I'd like to go to Bullet</p>

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<p style="text-align: right;">Page 442</p> <p>1 Point 1, summary of opinions. Bullet</p> <p>2 Point 1: "Cosmetic talc particles and</p> <p>3 non-asbestos cleavage fragments are</p> <p>4 different chemically, physically, and</p> <p>5 structurally from amphibole asbestos</p> <p>6 types, crocidolite and amosite."</p> <p>7 You mentioned cosmetic talc</p> <p>8 particles, but you have never studied</p> <p>9 cosmetic talc particles; is that correct?</p> <p>10 MR. FROST: Objection.</p> <p>11 THE WITNESS: Correct. But</p> <p>12 they are -- I again reviewed the</p> <p>13 IARC report and reports by</p> <p>14 Zazenski, et al., characterizing</p> <p>15 cosmetic talcs, and they are --</p> <p>16 that's where this statement came</p> <p>17 from.</p> <p>18 BY MR. SMITH:</p> <p>19 Q. And you mentioned</p> <p>20 crocidolite and amosite asbestos,</p> <p>21 correct?</p> <p>22 A. Yes.</p> <p>23 Q. And we mentioned earlier</p> <p>24 this is not the type of asbestos that's</p>	<p style="text-align: right;">Page 444</p> <p>1 reactions.</p> <p>2 Q. And analyzing whether a</p> <p>3 sample of materials is talc, asbestos, or</p> <p>4 talc with asbestos, you leave that to</p> <p>5 mineralogists, as we discussed that</p> <p>6 earlier, correct?</p> <p>7 A. Yes. I work with reference</p> <p>8 samples of materials.</p> <p>9 Q. And the same for determining</p> <p>10 if a mineral is asbestos or asbestiform,</p> <p>11 correct?</p> <p>12 MR. FROST: Objection.</p> <p>13 THE WITNESS: Yes. The</p> <p>14 mineralogists I collaborate with</p> <p>15 characterize these materials.</p> <p>16 BY MR. SMITH:</p> <p>17 Q. And you're not a geologist?</p> <p>18 A. That's correct.</p> <p>19 Q. And not a materials analyst,</p> <p>20 correct?</p> <p>21 A. Correct.</p> <p>22 Q. And you are not an expert in</p> <p>23 determining the flexibility or rigidity</p> <p>24 of asbestos or cleavage fragments,</p>
<p style="text-align: right;">Page 443</p> <p>1 been found in Baby Powder and Shower to</p> <p>2 Shower; is that correct?</p> <p>3 MR. FROST: Objection.</p> <p>4 THE WITNESS: Again, you're</p> <p>5 assuming that other asbestos types</p> <p>6 have been found in these</p> <p>7 materials, and I am unaware of</p> <p>8 that data.</p> <p>9 BY MR. SMITH:</p> <p>10 Q. Okay. Bullet Point 1, you</p> <p>11 mention the different chemical, physical,</p> <p>12 and structural differences of cosmetic</p> <p>13 talc and crocidolite asbestos and amosite</p> <p>14 asbestos, correct?</p> <p>15 MR. FROST: Objection.</p> <p>16 THE WITNESS: Yes.</p> <p>17 BY MR. SMITH:</p> <p>18 Q. And you stated you are not a</p> <p>19 mineralogist, correct?</p> <p>20 A. No, but I have interacted</p> <p>21 with mesothelial cell, let's say,</p> <p>22 biologists and geologists who have</p> <p>23 emphasized in their experiments or</p> <p>24 characterization that they're different</p>	<p style="text-align: right;">Page 445</p> <p>1 correct?</p> <p>2 MR. FROST: Objection.</p> <p>3 THE WITNESS: I have not</p> <p>4 used methods in my lab -- measure</p> <p>5 particle flexibility directly.</p> <p>6 BY MR. SMITH:</p> <p>7 Q. Let's go to Bullet Point 2.</p> <p>8 "Because of these different properties,</p> <p>9 cosmetic talc particles and non-asbestos</p> <p>10 cleavage fragments are unlikely to reach</p> <p>11 or be retained at sites of development of</p> <p>12 mesothelioma or ovarian cancers."</p> <p>13 You stated that you never</p> <p>14 studied cosmetic talc particles or</p> <p>15 cleavage fragments that have been</p> <p>16 reported in Baby Powder or Shower to</p> <p>17 Shower, correct?</p> <p>18 MR. FROST: Objection.</p> <p>19 THE WITNESS: I myself</p> <p>20 haven't studied them. But others</p> <p>21 have, and their properties have</p> <p>22 been documented by others,</p> <p>23 including mineralogists.</p> <p>24 BY MR. SMITH:</p>

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<p style="text-align: right;">Page 446</p> <p>1 Q. What is the basis of that</p> <p>2 statement?</p> <p>3 A. The basis of the statement</p> <p>4 is twofold. Cosmetic talc particles as</p> <p>5 defined in IARC are platelike, large</p> <p>6 platelike discs that would not be</p> <p>7 deposited as would amphibole asbestos</p> <p>8 types at the pleura. They would not make</p> <p>9 it out to the pleura because of their</p> <p>10 size. And this is true of non-asbestos</p> <p>11 cleavage fragments as well. Because</p> <p>12 experiments by Dr. Wiley have indicated</p> <p>13 that these cleavage fragments break</p> <p>14 perpendicular to the fiber surface. So</p> <p>15 they don't form long, thin fibers.</p> <p>16 And cleavage fragments of a</p> <p>17 size that are pathogenic; that is, 5 to</p> <p>18 10 microns are rare, if at all existent</p> <p>19 in diameters that would allow them to be</p> <p>20 taken out to the pleura by transfer or</p> <p>21 retained in the pleura.</p> <p>22 Q. You told me earlier in the</p> <p>23 depo that you had not studied how</p> <p>24 tremolite, anthophyllite, and actinolite</p>	<p style="text-align: right;">Page 448</p> <p>1 development of disease.</p> <p>2 BY MR. SMITH:</p> <p>3 Q. And you also stated earlier</p> <p>4 that you had not performed any studies on</p> <p>5 whether cleavage fragments can reach the</p> <p>6 area of the lung where -- where</p> <p>7 mesothelioma is induced and developed.</p> <p>8 We discussed that earlier.</p> <p>9 MR. FROST: Objection.</p> <p>10 THE WITNESS: That's true,</p> <p>11 but other individuals have shown</p> <p>12 that cleavage fragments of a</p> <p>13 variety of types are not</p> <p>14 mesothelioma-genic.</p> <p>15 BY MR. SMITH:</p> <p>16 Q. And what basis do you have</p> <p>17 to say that cosmetic-grade talc particles</p> <p>18 cannot be retained by the ovaries?</p> <p>19 MR. FROST: Objection.</p> <p>20 THE WITNESS: I am saying</p> <p>21 that there's no scientifically</p> <p>22 plausible pathway where they would</p> <p>23 be translocated in a retrograde</p> <p>24 fashion from the perineum to the</p>
<p style="text-align: right;">Page 447</p> <p>1 asbestos reached the areas of the lungs</p> <p>2 where mesothelioma is induced and</p> <p>3 developed, and you could not make a</p> <p>4 strict analogy to these type of asbestos</p> <p>5 from your study of other types of</p> <p>6 asbestos. We talked about that earlier</p> <p>7 in the deposition.</p> <p>8 MR. FROST: Objection.</p> <p>9 THE WITNESS: We did. But I</p> <p>10 want to emphasize that if these</p> <p>11 materials -- it's known that</p> <p>12 anthophyllite and tremolite are</p> <p>13 thicker, blunter fibers than the</p> <p>14 needlelike amphibole asbestos</p> <p>15 types and, therefore, their</p> <p>16 propensity to either reach or be</p> <p>17 retained at sites of development</p> <p>18 of mesothelioma would be related</p> <p>19 to their surface features, as well</p> <p>20 as their physical features and,</p> <p>21 therefore, them being blunt and</p> <p>22 thick, like cleavage fragments,</p> <p>23 they would be unlikely to reach or</p> <p>24 be retained at sites of</p>	<p style="text-align: right;">Page 449</p> <p>1 ovary.</p> <p>2 BY MR. SMITH:</p> <p>3 Q. Well, you state in your --</p> <p>4 in -- in the bullet point that fragments</p> <p>5 are unlikely to be reached -- reach or be</p> <p>6 retained by these sites of development of</p> <p>7 mesotheliomas or ovarian cancers. And</p> <p>8 I'm going to the or part. Or retained.</p> <p>9 What basis do you have to</p> <p>10 say that cosmetic-grade talc particles</p> <p>11 cannot be retained by the ovaries?</p> <p>12 MR. FROST: Objection.</p> <p>13 THE WITNESS: What I'm</p> <p>14 saying is that there has been no</p> <p>15 information suggesting that they</p> <p>16 get there to cause disease.</p> <p>17 BY MR. SMITH:</p> <p>18 Q. Have you not seen</p> <p>19 pathological studies of -- and we've gone</p> <p>20 through a bunch of them, where they have</p> <p>21 found talc in human ovarian tissue?</p> <p>22 MR. FROST: Objection.</p> <p>23 THE WITNESS: Yes, and I'd</p> <p>24 like to emphasize that the IARC</p>

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<p style="text-align: right;">Page 450</p> <p>1 committee found that talc degrades</p> <p>2 in a period of about eight years.</p> <p>3 So my point here is that</p> <p>4 we're talking about mesothelioma</p> <p>5 in this case, in my second bullet.</p> <p>6 And that they would not be</p> <p>7 retained for periods of time</p> <p>8 sufficient enough for the</p> <p>9 development of mesothelioma. We</p> <p>10 don't know what the latency period</p> <p>11 is of ovarian cancer.</p> <p>12 But the same thing is true,</p> <p>13 that the amphibole asbestos types</p> <p>14 that I've studied, crocidolite and</p> <p>15 amosite, are durable in lung for</p> <p>16 periods of time of decades, as</p> <p>17 opposed to years with something</p> <p>18 such as talc.</p> <p>19 BY MR. SMITH:</p> <p>20 Q. You understand about talc</p> <p>21 exposure, we're talking about chronic</p> <p>22 talc exposure over decades. Do you</p> <p>23 understand that that's what we are</p> <p>24 talking about?</p>	<p style="text-align: right;">Page 452</p> <p>1 particles in general showing that</p> <p>2 their half life in the human body</p> <p>3 is an approximately eight-year</p> <p>4 time span for a platelike talc.</p> <p>5 BY MR. SMITH:</p> <p>6 Q. But that's talking about</p> <p>7 dissolution, not about retention.</p> <p>8 A. But retention and</p> <p>9 dissolution are the same thing. If</p> <p>10 something dissolves, it can't be</p> <p>11 retained. It's one of the factors that's</p> <p>12 very important.</p> <p>13 Q. Do you know if any of those</p> <p>14 studies on bio durability have discussed</p> <p>15 or looked at talc in ovarian tissue to</p> <p>16 determine how long it survives in ovarian</p> <p>17 tissue?</p> <p>18 A. No. Because the studies</p> <p>19 that have shown it in ovarian tissues are</p> <p>20 for probably decades since these</p> <p>21 exposures. We have no idea. And the way</p> <p>22 to address that question wouldn't be in</p> <p>23 looking at human ovarian material.</p> <p>24 Q. You have not performed any</p>
<p style="text-align: right;">Page 451</p> <p>1 A. You may be talking about it,</p> <p>2 but I don't think there's evidence again</p> <p>3 showing that chronic talc exposure leads</p> <p>4 to migration to the ovary or that it's</p> <p>5 associated with -- with disease.</p> <p>6 Q. I'm just questioning your</p> <p>7 opinion about fragments are unlikely,</p> <p>8 non-asbestos cleavage fragments and</p> <p>9 cosmetic talc particles, to be retained</p> <p>10 at the sites of development of ovarian</p> <p>11 cancer.</p> <p>12 And I want to know what your</p> <p>13 basis of opinion that cosmetic-grade talc</p> <p>14 which you've never tested cannot be</p> <p>15 retained by the ovaries.</p> <p>16 MR. FROST: Objection.</p> <p>17 BY MR. SMITH:</p> <p>18 Q. When we have studies that</p> <p>19 show talc in human ovarian tissue and --</p> <p>20 and human cancer tissue.</p> <p>21 MR. FROST: Objection.</p> <p>22 THE WITNESS: So what I'm</p> <p>23 telling -- what I'm telling you is</p> <p>24 that there are studies on talc</p>	<p style="text-align: right;">Page 453</p> <p>1 studies on whether or not asbestos</p> <p>2 cleavage fragments can cause ovarian</p> <p>3 cancer, correct?</p> <p>4 MR. FROST: Objection.</p> <p>5 THE WITNESS: I have not.</p> <p>6 BY MR. SMITH:</p> <p>7 Q. Third bullet point. "Talc</p> <p>8 and non-asbestos cleavage fragments are</p> <p>9 not reactive with cells and their</p> <p>10 effective repair pathways occur. Because</p> <p>11 they are distinct in chemistry and other</p> <p>12 features from asbestos fibers, they do</p> <p>13 not have the same potential to cause the</p> <p>14 abnormal cell responses that are integral</p> <p>15 to the development of cancers."</p> <p>16 MR. FROST: Objection.</p> <p>17 BY MR. SMITH:</p> <p>18 Q. Is that your third bullet</p> <p>19 point in your summary of opinions?</p> <p>20 A. Yes.</p> <p>21 Q. Okay. Well, talc not being</p> <p>22 reactive with cells, we showed in Shukla</p> <p>23 that talc was reactive with cells by</p> <p>24 altering 30 genes at high concentrations</p>

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<p style="text-align: right;">Page 454</p> <p>1 at eight hours, right?</p> <p>2 A. And what I'm saying is that</p> <p>3 any particle would have caused those</p> <p>4 changes. That was inert. And the 30</p> <p>5 changes that we observed as opposed to</p> <p>6 hundreds of genes with asbestos was not</p> <p>7 significantly different than the</p> <p>8 responses of these cells to titanium</p> <p>9 dioxide or glass.</p> <p>10 Q. And we went over, titanium</p> <p>11 dioxide and glass did not alter any</p> <p>12 genes, correct?</p> <p>13 A. It did not alter any genes</p> <p>14 significantly. That's correct.</p> <p>15 Q. In regards to cleavage</p> <p>16 fragments, you stated you -- stated</p> <p>17 earlier you never studied anthophyllite</p> <p>18 or actinolite cleavage fragments, or</p> <p>19 tremolite --</p> <p>20 MR. FROST: Objection.</p> <p>21 BY MR. SMITH:</p> <p>22 Q. -- besides the one study in</p> <p>23 New York?</p> <p>24 A. I have studied survival and</p>	<p style="text-align: right;">Page 456</p> <p>1 theme is primarily the national</p> <p>2 institutes that conducts research.</p> <p>3 And this was a road plan for</p> <p>4 research.</p> <p>5 BY MR. SMITH:</p> <p>6 Q. Well, they talk about the</p> <p>7 NIOSH REL, correct, and exposure to EMPs</p> <p>8 that meet the definition of fibrous talc</p> <p>9 in this -- in this document; is that</p> <p>10 correct?</p> <p>11 MR. FROST: Objection.</p> <p>12 THE WITNESS: I -- you would</p> <p>13 have to show me where that's</p> <p>14 specifically. I don't remember</p> <p>15 fibrous talc being used as a term</p> <p>16 in this document.</p> <p>17 BY MR. SMITH:</p> <p>18 Q. Look on Page 33. Look at</p> <p>19 2.7.2, clarification of the current NIOSH</p> <p>20 REL. And it says at the top right</p> <p>21 column, "However, as the following</p> <p>22 clarified REL makes clear, particles that</p> <p>23 meet the specified dimensional criteria</p> <p>24 remain countable under the REL for the</p>
<p style="text-align: right;">Page 455</p> <p>1 toxicity of three samples of New York</p> <p>2 State talc containing non-asbestiform</p> <p>3 tremolite and non-asbestos anthophyllite.</p> <p>4 Q. And that was studying</p> <p>5 industrial-grade talc, correct?</p> <p>6 A. That is correct.</p> <p>7 Q. And we discussed what NIOSH</p> <p>8 was earlier. Do you recall? I think we</p> <p>9 went through what NIOSH was. It was</p> <p>10 under OSHA. Do you recall that</p> <p>11 testimony?</p> <p>12 A. NIOSH stands for the</p> <p>13 National Institute of Occupational Safety</p> <p>14 and Health, yes.</p> <p>15 MR. FROST: Talking about</p> <p>16 the roadmap?</p> <p>17 THE WITNESS: I got it here.</p> <p>18 BY MR. SMITH:</p> <p>19 Q. NIOSH regulates exposures to</p> <p>20 EMPs that meet the definition which may</p> <p>21 include fibrous talc; is that correct?</p> <p>22 MR. FROST: Objection.</p> <p>23 THE WITNESS: OSHA is the</p> <p>24 regulatory agency. NIOSH, in my</p>	<p style="text-align: right;">Page 457</p> <p>1 reasons stated above, even if they're</p> <p>2 derived from non-asbestiform analogs of</p> <p>3 the asbestiform minerals. With the use</p> <p>4 of terms defined in this roadmap, the</p> <p>5 NIOSH REL is now clarified as follows."</p> <p>6 And it talks about, "NIOSH</p> <p>7 has determined that exposure to asbestos</p> <p>8 fibers can cause cancer and asbestosis in</p> <p>9 humans and recommends exposure be reduced</p> <p>10 to the lowest feasible concentration.</p> <p>11 NIOSH has designated asbestos to be a</p> <p>12 potential carcinogen and recommends that</p> <p>13 exposures be reduced to the lowest</p> <p>14 feasible concentration.</p> <p>15 "NIOSH REL for airborne</p> <p>16 asbestos fibers and elongated mineral</p> <p>17 particles is .1 countable EMP from one or</p> <p>18 more covered minerals per cubic</p> <p>19 centimeter averaged over 100 minutes."</p> <p>20 And it talks about a</p> <p>21 countable elongated mineral particle,</p> <p>22 EMP. And then it goes on to the next</p> <p>23 page, next bullet point.</p> <p>24 "A covered mineral is any</p>



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<p>1 mineral having the crystal structure and 2 elemental composition of one of the 3 asbestos varieties (chrysotile), 4 riebeckite asbestos (crocidolite)", I 5 can't pronounce all of these. All the 6 different asbestos -- "or one of their 7 non-asbestiform analogs and the amphibole 8 minerals contained in the mineral series, 9 the tremolite mineral series" -- and I 10 can't pronounce those names. 11 Is that correct? 12 MR. FROST: Objection. 13 THE WITNESS: I'm not sure 14 what this is saying. It says 15 clarification -- it's under a 16 section, "Clarification of the 17 current exposure limit." They do 18 state on Page 32 that they suggest 19 that -- "Studies suggest that 20 non-asbestiform amphiboles might 21 post different risks than 22 asbestos," and that was a theme 23 throughout this document. 24 BY MR. SMITH:</p>	<p>1 Sciences. And that questioned 2 statements such as this and 3 clarified them in the response of 4 that committee. 5 So there -- I would disagree 6 that NIOSH -- and in fact, I have 7 been convinced through the decades 8 that OSHA and NIOSH don't regulate 9 non-asbestiform analogs. 10 BY MR. SMITH: 11 Q. So you're telling me, in 12 your opinion, you do not believe that 13 non-asbestos cleavage fragments are 14 subject to REL -- the count for REL 15 regarding the exposure limits to human 16 workers to non-asbestiform cleavage 17 fragments? You don't believe that that 18 exists today? 19 MR. FROST: Objection. 20 THE WITNESS: I'm sorry, the 21 question is, what exists? 22 BY MR. SMITH: 23 Q. A time-weighted limit called 24 an REL on exposures of U.S. workers to</p>
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<p>1 Q. Absolutely. But they also 2 regulate -- do you understand that NIOSH 3 and REL is a time-weighted average 4 exposure to a worker by a mineral? Do 5 you understand that? 6 MR. FROST: Objection. 7 THE WITNESS: I understand 8 it, but I -- 9 BY MR. SMITH: 10 Q. But my question. 11 A. -- do not -- 12 Q. Hold on. My question -- you 13 understand that. 14 My question is, do you 15 understand that non-asbestiform cleavage 16 fragments are regulated under the NIOSH 17 REL for exposures to human workers? 18 MR. FROST: Objection. 19 THE WITNESS: No. I don't 20 think that's correct. As a matter 21 of fact after this report, there 22 was another report to address the 23 roadmap's strengths and weaknesses 24 by the National Academy of</p>	<p>1 these cleavage fragments -- 2 MR. FROST: Objection. 3 BY MR. SMITH: 4 Q. -- by NIOSH? 5 A. I don't know what those are. 6 And they're not stated here. So I can't 7 give you a NIOSH REL for non-asbestos 8 cleavage fragments. 9 Q. You can't tell me whether 10 the NIOSH -- whether you count a worker's 11 exposure to non-asbestos cleavage 12 fragments -- goes to the overall exposure 13 of a worker for the NIOSH REL or not? 14 MR. FROST: Objection. 15 THE WITNESS: That is not my 16 area of expertise. No, I can't 17 tell you that. And I can just 18 tell you that biologically, as is 19 stated in this report, it's stated 20 that these cleavage fragments 21 might pose different risks or 22 lesser risks than their asbestos 23 counterparts. 24 BY MR. SMITH:</p>

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<p style="text-align: right;">Page 462</p> <p>1 Q. It doesn't say no risk. In 2 fact, they're regulated per the NIOSH 3 document that I just showed you. 4 MR. FROST: Objection. 5 THE WITNESS: I -- I would 6 have to see that, whether that 7 still exists. That was a subject 8 of controversy, not only in this 9 document, but in a subsequent 10 document that looked at the 11 deliberations of this committee. 12 BY MR. SMITH: 13 Q. The French government 14 doesn't agree with you on your assessment 15 of the health risk of cleavage fragments, 16 do they? 17 MR. FROST: Objection. 18 THE WITNESS: I think French 19 scientists agree with me. 20 BY MR. SMITH: 21 Q. You have been shown the 22 ANSES articles and the publication, have 23 you not, and the official opinion of the 24 French agency for food, environmental,</p>	<p style="text-align: right;">Page 464</p> <p>1 health issues by assessing health risk 2 and benefits, often through the prism of 3 the human and social sciences. 4 "Its monitoring, diligence, 5 and surveillance work provides input for 6 risk assessment. ANSES work fully 7 addresses all types of risk, chemical, 8 biological, physical, et cetera, to which 9 a person may be subjected intentionally 10 or otherwise at all ages and stages of 11 life, including through exposure at work, 12 while traveling, while engaging in 13 leisure activities or via their diet." 14 Do you see that? 15 A. And I state that I have 16 never heard of ANSES prior to this 17 litigation. 18 Q. Okay. And if you look at 19 the second page, it talks about the 20 collaborative, impartial expert 21 assessment that they do. And then I want 22 to -- 23 A. I've interacted with many 24 scientists, including the leading</p>
<p style="text-align: right;">Page 463</p> <p>1 and occupational health and safety? 2 A. That is not their 3 national -- Inserm is their national 4 research on fibers and particles. I have 5 no idea what ANSES is. 6 Q. Let's look at page -- at 7 document -- Exhibit 43. 8 (Document marked for 9 identification as Exhibit 10 Mossman-43.) 11 BY MR. SMITH: 12 Q. "The French Agency For Food, 13 Environmental, and Occupational Health 14 and Safety," A-N-S-E-S, "was created on 15 July 1st, 2010. It is an administrative 16 public establishment accountable to the 17 French Ministries of Health, Agriculture, 18 Environment, Labor and Consumer Affairs. 19 ANSES undertakes monitoring, expert 20 assessment, research, and reference 21 activities in a broad range of topics 22 that encompass human health, animal 23 health and wellbeing, and plant health. 24 It offers a cross-cutting perspective on</p>	<p style="text-align: right;">Page 465</p> <p>1 scientist in France at Inserm and never 2 have heard of this society or whatever it 3 is, an agency, and would question whether 4 it's a research agency. 5 (Document marked for 6 identification as Exhibit 7 Mossman-44.) 8 BY MR. SMITH: 9 Q. This is Exhibit 44. It's 10 the Director General of ANSES opinion. 11 It's an opinion of the French agency for 12 food, environmental and occupational 13 health and safety, on health effects 14 identified of cleavage fragments from -- 15 of amphiboles from quarried minerals. 16 It says, "ANSES undertakes 17 independent and pluralistic scientific 18 expert assessments. ANSES ensures 19 environmental, occupational and food 20 safety as well as assessing the potential 21 health risks they may entail. It also 22 contributes to the protection of the 23 health and welfare of animals, the 24 protection of plant health and the</p>

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<p style="text-align: right;">Page 466</p> <p>1 evaluation of the nutritional 2 characteristics of food. It provides the 3 competent authorities with all necessary 4 information concerning these risks as 5 well as the requisite expertise and 6 scientific and technical support for 7 drafting legislative and statutory 8 provisions and implementing risk 9 management societies." And for -- it 10 cites the French Public Health Code. 11 The opinions are made 12 public. And it states, "On August 28, 13 2014, ANSES was requested by the 14 Directorate General for Labour, the 15 Directorate General for Risk 16 Protection" -- "Prevention and 17 Directorate General for Health to 18 undertake the following expert appraisal: 19 Health effects and identification of 20 cleavage fragments of amphiboles from 21 quarried minerals." 22 And it goes on, the second 23 page, it says, "Against this background 24 the request included the following</p>	<p style="text-align: right;">Page 468</p> <p>1 document before? 2 MR. FROST: Objection. 3 THE WITNESS: I have. 4 Am I allowed to comment on 5 it? 6 MR. FROST: My objection was 7 to reading it. 8 THE WITNESS: Okay. 9 BY MR. SMITH: 10 Q. And then if you go onto the 11 page -- let's see. Seven pages in. It 12 says, "To sum up, the CES concludes that: 13 "In the current state of 14 knowledge concerning their health 15 effects, cleavage fragments of 16 non-asbestos amphiboles, actinolite, 17 anthophyllite, tremolite, grunerite and 18 riebeckite were meet" -- "meeting the 19 WHO's dimensional criteria for fibers 20 should not be distinguished from their 21 asbestiform counterparts." 22 And do you see that written 23 there? 24 Do you agree with that</p>
<p style="text-align: right;">Page 467</p> <p>1 points: 2 "To review toxicological and 3 epidemiological evidence relating to 4 cleavage fragments of minerals with 5 non-asbestiform profiles: Actinolite, 6 anthophyllite, tremolite, grunerite, 7 riebeckite. What conclusions can be 8 reached about their effects on health? 9 "2, what current data are 10 available regarding the specific 11 exposures to cleavage fragments and 12 minerals cited above? 13 "3, are there routine 14 analytics methods that can be implemented 15 by laboratories accredited, capable of 16 distinguishing the fibers?" And -- and 17 they list the fibers there. 18 And it says, "On the 19 conclusion of the expert appraisal, 20 recommendations may be proposed 21 concerning the protection and prevention 22 of risks to health of persons exposed to 23 these cleavage fragments." 24 Have you ever seen this</p>	<p style="text-align: right;">Page 469</p> <p>1 assessment by them? 2 A. Can you point to the -- 3 MR. FROST: Objection. 4 THE WITNESS: -- statement 5 on Page 7 that you're talking 6 about? 7 There is no reason to make a 8 distinction? Is that what you're 9 talking about? 10 BY MR. SMITH: 11 Q. That statement right here. 12 It's, to sum up, the CES concludes that. 13 A. First of all, I don't know 14 what the CES is. This report was signed 15 by one individual. I have never heard of 16 this review or this assignment through a 17 scientific body. 18 And I also want to emphasize 19 that the references that are cited, if 20 you look at Page 12 and 13, their total 21 for this entire document of 14 or so 22 references, of which many are original 23 ANSES studies which appear to be related 24 to outcrops of asbestos.</p>

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<p>1 But more importantly, the</p> <p>2 references they cite, by Addison and</p> <p>3 McConnell, by Cyphert, by Davis, by</p> <p>4 Ilgren, Kodavanti, by me, who my name is</p> <p>5 spelled wrong. But we know that all of</p> <p>6 these, and Williams, all say that</p> <p>7 cleavage fragments do not pose a cancer</p> <p>8 risk.</p> <p>9 So this study, or whatever</p> <p>10 it was, the conclusions of this</p> <p>11 individual, are not based upon the</p> <p>12 peer-reviewed scientific literature that</p> <p>13 is cited.</p> <p>14 Q. So you disagree with their</p> <p>15 opinions about cleavage fragments?</p> <p>16 A. I do. It's not supported by</p> <p>17 their own references.</p> <p>18 Q. Okay. I want to show you an</p> <p>19 e-mail which I'm attaching as Exhibit 45.</p> <p>20 (Document marked for</p> <p>21 identification as Exhibit</p> <p>22 Mossman-45.)</p> <p>23 BY MR. SMITH:</p> <p>24 Q. Series of e-mails. I want</p>	<p>1 cleavage fragments ought not to be</p> <p>2 treated as asbestos.' Confusion and</p> <p>3 misinformation persists. John Kelse" --</p> <p>4 who you know, correct?</p> <p>5 A. I -- I knew him in the early</p> <p>6 1990s.</p> <p>7 Q. -- "sets out the facts for</p> <p>8 non-asbestiform amphiboles, reviews</p> <p>9 recent cases and warns against unreasoned</p> <p>10 decisionmaking."</p> <p>11 And he worked for who, who</p> <p>12 did John Kelse work for?</p> <p>13 A. When I corresponded with</p> <p>14 him, I believe he worked for</p> <p>15 R.T. Vanderbilt, but I'm not certain</p> <p>16 whether that was his lifetime employer or</p> <p>17 not. I have no idea.</p> <p>18 Q. Says, "I can see how it</p> <p>19 would be helpful, part of the ongoing</p> <p>20 self-education process for ourselves and</p> <p>21 our business partners to have something</p> <p>22 like this as a reference. But I defer to</p> <p>23 the experts like yourselves and advise if</p> <p>24 you feel the article is accurate, helpful</p>
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<p>1 you to go to the second page. It's by</p> <p>2 Rich Zazenski.</p> <p>3 Well, I want you to read the</p> <p>4 whole thing. Let's start at the -- it's</p> <p>5 going --</p> <p>6 A. Okay.</p> <p>7 Q. You are going to go to the</p> <p>8 back forward.</p> <p>9 A. Okay.</p> <p>10 MR. FROST: Objection.</p> <p>11 BY MR. SMITH:</p> <p>12 Q. And it's Peter Argust,</p> <p>13 director of regulatory affairs from Rio</p> <p>14 Tinto Minerals.</p> <p>15 And it states -- from Peter</p> <p>16 Argust to Rich Zazenski and Julie Pier</p> <p>17 and some others, regarding the article of</p> <p>18 industrial minerals asbestos.</p> <p>19 Julie -- "Rich, Julie, and</p> <p>20 Greg, our colleagues, Miguel Galindo has</p> <p>21 shared with me the attached article in</p> <p>22 Industrial Minerals magazine's</p> <p>23 February 2008 edition. The subtitle, '15</p> <p>24 years after OSHA ruled that common</p>	<p>1 or not. Could you give me your</p> <p>2 professional reactions. Thanks and kind</p> <p>3 regards, Peter, Peter Argust."</p> <p>4 Then the response is from</p> <p>5 Rich Zazenski at -- regulatory affairs</p> <p>6 manager at Rio Tinto Minerals. And he's</p> <p>7 got richzazenski@Luzenac.com as his</p> <p>8 e-mail address.</p> <p>9 He says, "I had seen and</p> <p>10 read this article, and my first reaction</p> <p>11 was 'who really wrote this paper for</p> <p>12 John's signature?' I know John. He is a</p> <p>13 fairly technical person, but excuse me,</p> <p>14 he would not write such an article and</p> <p>15 cite 129 references. The answer is</p> <p>16 obvious, regardless I cannot agree with</p> <p>17 his position. We just don't have enough</p> <p>18 facts. Geologically it doesn't make</p> <p>19 sense to me that you can have a mineral</p> <p>20 deposit that just contains</p> <p>21 non-asbestiform tremolite.</p> <p>22 "I believe the USGS study of</p> <p>23 talc from Death Valley, California,</p> <p>24 nailed it correctly. That if a deposit</p>

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<p style="text-align: right;">Page 474</p> <p>1 contains 'non-asbestiform' tremolite, 2 there is also asbestiform tremolite 3 naturally present as well. And since 4 tremolite was never really a large 5 commercial mineral such as chrysotile or 6 crocidolite, there is not enough medical 7 data to conclude that 'blocky' tremolite 8 is simply a nuisance dust. 9 "But that has been the story 10 line for Vanderbilt for years and they 11 are sticking to it. I closely followed 12 the OSHA/Vanderbilt debate during the 13 1990s. Essentially OSHA 'threw in the 14 towel,' rather than expend their limited 15 resources on this issue. Their decision 16 by no means should be interpreted as a 17 vindication of Vanderbilt's arguments. 18 "Back in the late 1970s and 19 1980s, other talc companies were 20 distancing themselves from any deposit 21 that contained tremolite and of" -- "all, 22 of course, but Vanderbilt. They" -- 23 "Then they proceeded to poison the well." 24 Then the last e-mail is from</p>	<p style="text-align: right;">Page 476</p> <p>1 listed on here. So I guess I'm 2 missing the point of this. 3 What I stated is that my 4 research, animal studies, and OSHA 5 still to this day agree that 6 cleavage fragments do not pose the 7 same health risks as their 8 asbestiform counterparts. 9 BY MR. SMITH: 10 Q. Do you believe they pose any 11 health risk? 12 MR. FROST: Objection. 13 THE WITNESS: Well, 14 that's -- that's subjective. 15 Certainly with regard to 16 mesothelioma, no. There have been 17 many studies, including recent 18 ones from the EPA, that argue 19 against cleavage fragments as 20 causing cancer in animals. 21 BY MR. SMITH: 22 Q. What about ovarian cancer? 23 MR. FROST: Objection. 24 THE WITNESS: There in all</p>
<p style="text-align: right;">Page 475</p> <p>1 Michelle -- I can't pronounce her last 2 name, from Rio Tinto Minerals, sent on 3 January 31st, 2008. And it said, "Dear 4 all, I agree with Rich's position." 5 So regarding cleavage 6 fragments and their ill health effects, 7 you had the employee of Luzenac, who was 8 head of regulatory affairs -- he was the 9 regulatory affairs manager, Rich 10 Zazenski, disagreeing with your position; 11 is that correct? 12 MR. FROST: Objection. I'll 13 just object to reading the e-mail 14 in, but... 15 THE WITNESS: He was 16 disagreeing with my position on? 17 BY MR. SMITH: 18 Q. On the ill health effects of 19 asbestos -- excuse me -- of cleavage 20 fragments on exposures. 21 MR. FROST: Objection. 22 THE WITNESS: Yeah, I'm not 23 sure what this correspondence is. 24 I have not -- I don't think I'm</p>	<p style="text-align: right;">Page 477</p> <p>1 of the experiments with cleavage 2 fragments in animals, ovarian 3 cancers have not developed. 4 BY MR. SMITH: 5 Q. Well, tell me what studies 6 have studied cleavage fragments in their 7 relation to ovarian cancer. 8 A. What I'm saying is that 9 cleavage fragments, by a variety of 10 routes, inhalation, intrapleural 11 injection, intraperitoneal, have not 12 developed -- have not resulted in the 13 development of ovarian cancers in 14 animals. Hundreds of -- 15 Q. Tell me the study that 16 studied cleavage fragments and their 17 relationship to ovarian cancer. 18 MR. FROST: Objection. 19 BY MR. SMITH: 20 Q. I want the specific study 21 that you're referencing. 22 A. That's not what I said. I'm 23 saying that cleavage fragments of a 24 variety of types have been assessed in</p>



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<p>1 lifetime studies with animals, including 2 studies with tremolite asbestos and 3 tremolite non-asbestos cleavage 4 fragments. 5 None of those studies have 6 ovarian cancer develop with either 7 asbestos other cleavage fragments. 8 Q. Have you -- do you know if 9 even ovarian cancer was looked for in 10 those studies? 11 MR. FROST: Objection. 12 THE WITNESS: These are 13 lifetime studies -- 14 BY MR. SMITH: 15 Q. Which studies? I need the 16 names of them. 17 MR. FROST: Objection. 18 THE WITNESS: Okay. Well, I 19 suggest that there -- many of them 20 are in my expert report. The ones 21 that I can think of are 22 Drs. Coffin at the EPA, recent 23 studies by Cyphert, C-Y-P-H-E-R-T, 24 who looked at ferro-actinolite</p>	<p>1 of them may be summarized in IARC. 2 BY MR. SMITH: 3 Q. All right. Let's move on. 4 Bullet Point 4. "Trace amounts of 5 cleavage fragments or other minerals may 6 be present in industrial and cosmetic 7 talcs have little or no chemical 8 biological reactivity." 9 We've gone through, I think, 10 some studies just a minute ago about 11 French government and NIOSH, and I'm 12 going to leave that bullet point alone. 13 A. Okay. 14 Q. Next bullet point. The 15 numerous -- "The results of numerous 16 epidemiological and experimental studies 17 assessing carcinogenic potential short 18 asbestos support the concept that short 19 fibers and cleavage fragments, even of 20 respirable dimensions, do not play a role 21 in the induction of tumors." 22 You have not looked at Longo 23 or Rigler's testing or any internal 24 documents about what asbestos has been</p>
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<p>1 cleavage fragments. 2 BY MR. SMITH: 3 Q. And ovarian cancer? 4 A. What I'm telling you is that 5 people have not looked at ovarian cancer 6 and done studies and said, we're going to 7 expose animals and see whether they get 8 ovarian cancers. What they have looked 9 at have been lifetime studies in a 10 variety of organs and has not -- these 11 have not indicated that ovarian cancers 12 are a signature of cleavage fragments, 13 regardless of how much was instilled and 14 regardless of the route of administration 15 over the lifetime of the animals, all of 16 whom who were autopsied at death. 17 Q. Do you know any of those 18 that specifically looked at exposing 19 cleavage fragments and then -- to ovarian 20 tissue to determine whether they were 21 carcinogenic or had carcinogenic 22 properties to the ovaries? 23 MR. FROST: Objection. 24 THE WITNESS: I believe some</p>	<p>1 found in Baby Powder or Shower to Shower, 2 correct? 3 MR. FROST: Objection. 4 THE WITNESS: Yes. This is 5 not relevant to this, my 6 conclusions here. My conclusions 7 in terms of epidemiology and 8 experimental studies are based 9 upon the peer-reviewed scientific 10 literature and do not support the 11 concept that short fibers or 12 cleavage fragments play a role in 13 the induction of mesotheliomas or 14 ovarian cancers. 15 BY MR. SMITH: 16 Q. Well -- 17 A. And those are all referenced 18 within the report. 19 Q. Well, my point -- what I was 20 trying to get to, my second question is, 21 you don't know the fiber size or length 22 of asbestos found in these Baby Powder 23 bottles or Shower to Shower bottles. You 24 haven't seen the studies.</p>

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<p style="text-align: right;">Page 482</p> <p>1 MR. FROST: Objection to 2 form. 3 THE WITNESS: Again, sir, it 4 doesn't make any difference. All 5 of these studies and use of these 6 materials, regardless of their 7 source, were covered by cohort 8 studies with women looking at talc 9 exposures. And none of these have 10 shown convincing or statistical 11 increase in risk, and they haven't 12 indicated dose-response or 13 frequency effect. 14 So if they -- if there were 15 fibers there, such as asbestos 16 fibers in trace amounts or small 17 amounts, it still -- it wasn't 18 reflected at an increased 19 incidence of disease. 20 BY MR. SMITH: 21 Q. Fifth bullet point, 22 "Experimental studies demonstrate no 23 adverse effect levels from exposure to 24 certain concentrations of asbestos</p>	<p style="text-align: right;">Page 484</p> <p>1 effects document. These were summarized 2 in 1990. 3 Q. Well, you told me earlier 4 that you had not performed any studies on 5 those particular types of asbestos. 6 MR. FROST: Objection. 7 THE WITNESS: These are not 8 my studies. They are studies 9 where individuals have added 10 fibers of a variety of types of 11 asbestos to cells and have shown 12 that threshold levels exist below 13 which biological effects 14 indicative of tumor formation do 15 not occur. 16 BY MR. SMITH: 17 Q. As we discussed earlier, the 18 levels of exposure of each type of 19 asbestos in cosmetic-grade talc in terms 20 of human risk are outside your area of 21 expertise, correct? 22 MR. FROST: Objection. 23 THE WITNESS: Could you slow 24 down and --</p>
<p style="text-align: right;">Page 483</p> <p>1 fibers, indicating the existence of a 2 threshold for cancer causation below 3 which tumors do not develop." 4 None of the studies that you 5 cite for support of this opinion deal 6 with tremolite, anthophyllite, or 7 actinolite, correct? 8 MR. FROST: Objection. 9 THE WITNESS: I'd have to go 10 back and look at -- the 11 experimental studies that I'm 12 talking about are my own with 13 inhalation. And there are a 14 variety of studies with thresholds 15 in vitro that I summarize in a 16 2018 publication. 17 BY MR. SMITH: 18 Q. But they don't deal with 19 tremolite asbestos, anthophyllite 20 asbestos, or actinolite asbestos; is that 21 correct? 22 A. I'd have to go back and 23 look. Some of them might -- may have 24 dealt with tremolite in the health</p>	<p style="text-align: right;">Page 485</p> <p>1 BY MR. SMITH: 2 Q. As we discussed earlier, the 3 levels of exposure of each type of 4 asbestos in cosmetic-grade talc in terms 5 of human risk are outside of your area of 6 expertise, we talked about that earlier, 7 correct? 8 MR. FROST: Objection. 9 THE WITNESS: And, again, I 10 emphasize that it doesn't make any 11 difference what their levels would 12 be, in -- historically in talcum 13 powder if individuals using these 14 products did not develop ovarian 15 cancers. 16 BY MR. SMITH: 17 Q. All right. Let's go to -- 18 as far as the money that you've been 19 paid, how much -- much for J&amp;J have they 20 paid you totally, not just from the MDL? 21 How much have you made in 22 talc litigation, not just from the MDL, 23 do you know? 24 A. From J&amp;J, no, I would have</p>

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<p>1 no idea.</p> <p>2 Q. Can we get that, can you get</p> <p>3 that figure together and give it to your</p> <p>4 attorneys to give to us? Because I want</p> <p>5 the answer to that.</p> <p>6 A. Sure. What -- what</p> <p>7 information would you like?</p> <p>8 Q. How much you have made from</p> <p>9 Johnson &amp; Johnson in total, not just from</p> <p>10 the MDL, and how much money have you made</p> <p>11 since 2014 working in talc litigation.</p> <p>12 A. For Johnson &amp; Johnson?</p> <p>13 Okay.</p> <p>14 MR. FROST: You can follow</p> <p>15 up with a letter, we'll take it</p> <p>16 under advisement.</p> <p>17 THE WITNESS: Yeah. That's</p> <p>18 fine.</p> <p>19 MS. O'DELL: Thank you.</p> <p>20 THE WITNESS: Mm-hmm.</p> <p>21 BY MR. SMITH:</p> <p>22 Q. You talked about Shih</p> <p>23 earlier. Is it your belief that this</p> <p>24 study tested Johnson &amp; Johnson talc?</p>	<p>1 BY MR. SMITH:</p> <p>2 Q. That's not -- it's</p> <p>3 nonresponsive. That's all I needed to</p> <p>4 know.</p> <p>5 A. Okay.</p> <p>6 Q. Have you spoken to Dr. Shih</p> <p>7 about this case?</p> <p>8 A. I have not.</p> <p>9 Q. Have you communicated with</p> <p>10 Dr. Ann Wiley about this case?</p> <p>11 A. Not this case, no.</p> <p>12 Q. When was the last time you</p> <p>13 spoke to her?</p> <p>14 A. Spoke to her? I would say</p> <p>15 probably last November at a meeting. A</p> <p>16 scientific meeting.</p> <p>17 Q. Have you discussed her depo</p> <p>18 with her?</p> <p>19 A. My depo?</p> <p>20 Q. Hers.</p> <p>21 A. No, I haven't read her depo.</p> <p>22 Q. Have you discussed your depo</p> <p>23 with her?</p> <p>24 A. No.</p>
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<p>1 A. The studies that I saw by</p> <p>2 Shih --</p> <p>3 Q. It was an expert report.</p> <p>4 MR. FROST: Objection.</p> <p>5 THE WITNESS: It was an --</p> <p>6 let me emphasize. It was a</p> <p>7 scientific study where incipient,</p> <p>8 what are called pre-neoplastic</p> <p>9 lesions in the serous location --</p> <p>10 BY MR. SMITH:</p> <p>11 Q. Now, I'm -- Doctor, specific</p> <p>12 to my -- I'm sorry, I'm short on time. I</p> <p>13 need you to answer the question directly.</p> <p>14 Is it your belief that the</p> <p>15 study, the Shih study, the expert report</p> <p>16 that we discussed earlier that you said</p> <p>17 was a whiz-bang expert report, is it your</p> <p>18 belief that this -- this report tested</p> <p>19 J&amp;J talc?</p> <p>20 MR. FROST: Objection.</p> <p>21 THE WITNESS: I did not look</p> <p>22 at that information. These I</p> <p>23 believe were lesions from</p> <p>24 individuals with premalignant --</p>	<p>1 Q. Have you spoken or</p> <p>2 communicated with Dr. Laura Webb about</p> <p>3 this case?</p> <p>4 A. No, I have not.</p> <p>5 Q. She is a geologist here at</p> <p>6 the University of Vermont?</p> <p>7 A. Yes, I've met her before.</p> <p>8 Q. Have you communicated with</p> <p>9 Dr. Melinda Darby Dyar?</p> <p>10 A. I don't know that</p> <p>11 individual.</p> <p>12 Q. Heavy metals, nickels. What</p> <p>13 is the mechanism by which it causes</p> <p>14 cancer? Is it in connection?</p> <p>15 MR. FROST: Objection.</p> <p>16 THE WITNESS: Nickel?</p> <p>17 BY MR. SMITH:</p> <p>18 Q. Yes.</p> <p>19 A. It's particulate nickel.</p> <p>20 And no, it's generally through DNA</p> <p>21 damage. Nickel has a lot of effects on</p> <p>22 cells.</p> <p>23 Q. Can other heavy metals cause</p> <p>24 inflammation in tissues, such as</p>

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<p>1 chromium, cobalt, arsenic?</p> <p>2 A. Any material at a high</p> <p>3 enough concentration is going to cause</p> <p>4 inflammation, whether it's pathogenic or</p> <p>5 not.</p> <p>6 Q. Can heavy metals be</p> <p>7 cocarcinogens?</p> <p>8 MR. FROST: Objection.</p> <p>9 THE WITNESS: With cigarette</p> <p>10 smoke or other agents, I am sure</p> <p>11 there's data out there. I have</p> <p>12 not reviewed it. I can't give you</p> <p>13 an affirmative -- or a yes or no</p> <p>14 on that.</p> <p>15 BY MR. SMITH:</p> <p>16 Q. And Bob Glenn, I saw in some</p> <p>17 of your notes. He testified that "if</p> <p>18 there were fiber" -- "were a fiber of</p> <p>19 asbestos in talcum-based products, it</p> <p>20 would certainly provide a biologically</p> <p>21 plausible mechanism for increased lung</p> <p>22 disease, and that he suspected it would</p> <p>23 also have similar mechanism of disease in</p> <p>24 other tissues and organs."</p>	<p>1 Health Part A.</p> <p>2 Do you recall that?</p> <p>3 A. Yes. This is a paper that</p> <p>4 was presented at a conference of which</p> <p>5 the journal published the conference</p> <p>6 paper. So it wouldn't be through a --</p> <p>7 let's say a review -- review process as</p> <p>8 would -- I would have done for a</p> <p>9 high-impact journal. It was a --</p> <p>10 (Document marked for</p> <p>11 identification as Exhibit</p> <p>12 Mossman-46.)</p> <p>13 BY MR. SMITH:</p> <p>14 Q. Well, here is the impact</p> <p>15 factor during the year that you published</p> <p>16 Hillegass, which was 1.637. Do you see</p> <p>17 that? Look at the screen.</p> <p>18 MR. FROST: Objection.</p> <p>19 THE WITNESS: Yeah, that --</p> <p>20 that could have been. This was a</p> <p>21 journal that was used by the EPA</p> <p>22 scientists for meetings, and as I</p> <p>23 emphasize, the original data in</p> <p>24 that paper was --</p>
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<p>1 Do you agree with him?</p> <p>2 MR. FROST: Objection.</p> <p>3 THE WITNESS: I believe that</p> <p>4 was a misquote in Dr. Zelikoff's</p> <p>5 report.</p> <p>6 BY MR. SMITH:</p> <p>7 Q. All right. Let's go to your</p> <p>8 report real quick.</p> <p>9 You stated -- there was a</p> <p>10 criticism of Dr. Saed about the</p> <p>11 low-impact journal. You said you put his</p> <p>12 impact journal figures out about his</p> <p>13 publication. Do you recall that? And it</p> <p>14 was 2.548; is that right?</p> <p>15 A. No, I didn't put his impact</p> <p>16 figure out there. I provided a table of</p> <p>17 impact factors.</p> <p>18 Q. Okay. And regardless it's</p> <p>19 in your report, correct?</p> <p>20 A. I have a table of impact</p> <p>21 factors, yes, in my report.</p> <p>22 Q. Okay. And your -- the</p> <p>23 Hillegass study was published in the</p> <p>24 Journal of Toxicology and Environmental</p>	<p>1 MR. SMITH: How much time I</p> <p>2 got?</p> <p>3 THE WITNESS: -- reported by</p> <p>4 Dr. Shukla.</p> <p>5 BY MR. SMITH:</p> <p>6 Q. Okay.</p> <p>7 A. So this was a conference</p> <p>8 paper.</p> <p>9 Q. I want to go to your report.</p> <p>10 And on Page 10, it says, "Anatomy of the</p> <p>11 Female Reproductive Parts And Barriers To</p> <p>12 Particles."</p> <p>13 It says, "As illustrated in</p> <p>14 Figure 3 below, the extended genitalia</p> <p>15 are the first line of defense in that</p> <p>16 'the skin constitutes a relatively</p> <p>17 impenetrable barrier to most</p> <p>18 microorganisms unless breached by injury</p> <p>19 such as abrasion or burning.'"</p> <p>20 You believe that the female</p> <p>21 reproductive tract, there's an</p> <p>22 impenetrable barrier?</p> <p>23 MR. FROST: Objection.</p> <p>24 THE WITNESS: I think --</p>

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<p style="text-align: right;">Page 494</p> <p>1 what I'm emphasizing here, and 2 this is a book that actually has 3 been used to tutor individuals in 4 basic pathology, that the skin is 5 an impenetrable barrier to 6 particulate matter. 7 BY MR. SMITH: 8 Q. Okay. Let's go to the next 9 page. It talks about "ovarian cancer" -- 10 "cancers develop from epithelial cells 11 that line the ovaries and oviducts, 12 fallopian tubes. These structures are 13 surrounded by a protected fibrous 14 capsule." 15 What fibrous capsule is 16 around human ovarian -- ovaries? 17 MR. FROST: Objection. 18 THE WITNESS: So the ovarian 19 epithelium is lined by something 20 called the submucosal or the 21 interstitium. And that's 22 comprised of blood vessels and 23 fibers, meaning fibers from the 24 stroma. So this is called a</p>	<p style="text-align: right;">Page 496</p> <p>1 or not he used fallopian tubes cells in 2 his study? 3 A. It may have been one of the 4 lines that he looked at, but whether they 5 were normal or whether it was his one 6 normal line -- 7 Q. Do you know? 8 A. -- it is unclear. No. 9 Q. Did you have -- do you have 10 the capability of replicating Dr. Saed's 11 study if you wanted to try to replicate 12 it? 13 MR. FROST: Objection. 14 THE WITNESS: I wouldn't 15 want to. 16 BY MR. SMITH: 17 Q. Could you replicate it? 18 MR. FROST: Objection. 19 BY MR. SMITH: 20 Q. Could you do it? 21 A. I wouldn't do it the same 22 way he did it. 23 Q. I don't -- that's not what 24 I'm asking. I'm asking, could you</p>
<p style="text-align: right;">Page 495</p> <p>1 protective fibrous capsule. 2 Similar to the -- the lung 3 epithelium, which has a supportive 4 fibrous capsule under it, called 5 the interstitium. It's sometimes 6 called the stroma. 7 BY MR. SMITH: 8 Q. Do you know what -- we did 9 the conversion charts of -- well, do you 10 know the concentration levels that 11 Dr. Saed used in his study? 12 A. That was very difficult to 13 discern. 14 Q. Okay. Do you know -- did 15 you know -- did you see if Dr. Saed used 16 normal epithelial cells? 17 A. If he did, the -- 18 Q. Do you know if he did or 19 not? 20 MR. FROST: Objection. 21 THE WITNESS: I doubt very 22 much he did. 23 BY MR. SMITH: 24 Q. Okay. Do you know whether</p>	<p style="text-align: right;">Page 497</p> <p>1 replicate it if I asked you to do it? 2 MR. FROST: Objection. 3 BY MR. SMITH: 4 Q. Do you have the ability to 5 do it? 6 A. As he did, there are so many 7 flaws in his methodology, I just don't 8 know where to start. I mean, if we had 9 two hours, fine. 10 Q. My question is very simple. 11 If you had the -- do you have the 12 capability of replicating his study? Yes 13 or no? 14 MR. FROST: Objection. 15 THE WITNESS: I wouldn't 16 want to. And it has -- when you 17 say replicate -- 18 BY MR. SMITH: 19 Q. If you just followed exactly 20 what he did in his study, could you do 21 exactly what he did if I told you to do 22 exactly what he did in his study? 23 A. I wouldn't -- I wouldn't do 24 it.</p>



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<p>1 Q. That's not what I'm asking. 2 I'm saying could you? Do you have the 3 ability to do it? 4 A. As he did it? 5 Q. Again, I -- do you have the 6 ability to replicate his study? Yes or 7 no? 8 MR. FROST: Objection. 9 THE WITNESS: Based upon how 10 he describes it, no, there's not 11 enough detail there. 12 BY MR. SMITH: 13 Q. Okay. 14 A. And there's so many flaws. 15 Q. Did you attempt to replicate 16 his study and -- did you attempt to 17 replicate his study? 18 A. You mean I would actually 19 perform that study -- 20 Q. Yep. 21 A. -- as he did? 22 Q. Yep. 23 A. No. I wouldn't bother, 24 because it doesn't tell you anything.</p>	<p>1 THE WITNESS: They are 2 Vermont and Italian talc sources 3 from which Johnson's material may 4 have come from. 5 BY MR. SMITH: 6 Q. May have? 7 A. I don't know the details on 8 that. 9 Q. Okay. All right. Next 10 page, Page 29. You have Karageorgi 11 listed. And it says, "This group studied 12 the possible relationship between use of 13 talcum powder and endometrial cancer." 14 Do you see that? 15 A. Yes. 16 Q. And you say, "This group 17 found no statistical association and 18 concluded that future studies were 19 needed." You're saying that the 20 Karageorgi found no statistical 21 association between talcum powder and 22 endometrial cancer risk? Is that what 23 the conclusion of this study was? 24 A. I'd have to go back and look</p>
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<p>1 Q. You have a statement on Page 2 28. You have two studies cited for there 3 not being talc -- I mean, excuse me, 4 asbestos in Baby Powder. And that is 5 Boundy and Pira. 6 Do you see that on Page 28, 7 first bullet point? 8 A. These are studies on the 9 workers that were exposed to these talcs. 10 Q. Is that your basis that 11 there is not asbestos in Baby Powder or 12 Shower to Shower? 13 MR. FROST: Objection to 14 form. 15 THE WITNESS: It was stated 16 in these industrial talcs that 17 they were not associated with 18 asbestos contamination. 19 BY MR. SMITH: 20 Q. Those are industrial talcs, 21 not cosmetic-grade talcs. You understand 22 Baby Powder and Shower to Shower are 23 cosmetic-grade talcs, ma'am, don't you? 24 MR. FROST: Objection.</p>	<p>1 at it. It dealt with endometrial 2 cancers. I'd have to go back and review 3 it. 4 Dr. Saed stated it had -- 5 that it studied ovarian cancer, and that 6 was not the case. 7 Q. That's not my question to 8 you, Doctor. My question to you is, did 9 the study conclude that there was no 10 statistical association found between 11 talcum powder use and endometrial cancer? 12 MR. FROST: Objection. 13 THE WITNESS: It -- I 14 believe that it stated there might 15 be a risk, but future studies were 16 merited. I don't recall it 17 without looking at the -- 18 (Document marked for 19 identification as Exhibit 20 Mossman-47.) 21 BY MR. SMITH: 22 Q. This is the next numbered 23 exhibit, 47. 24 A. -- conclusions.</p>

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<p>1 Q. And this is that study?</p> <p>2 A. Okay.</p> <p>3 Q. And we go to conclusions</p> <p>4 right at the first of the abstract. "Our</p> <p>5 results suggest that perineal talcum</p> <p>6 powder use increases the risk of</p> <p>7 endometrial cancer, particularly around</p> <p>8 postmenopausal women."</p> <p>9 Attach that as Exhibit 47.</p> <p>10 MR. FROST: Objection. I</p> <p>11 don't know that there's a question</p> <p>12 there.</p> <p>13 BY MR. SMITH:</p> <p>14 Q. Well, obviously, that's</p> <p>15 different than what you put in your</p> <p>16 report on Page 29, correct?</p> <p>17 A. The reason I put it in my</p> <p>18 report is that Dr. Saed said that this is</p> <p>19 a study linking perineal use of talcum</p> <p>20 powder to ovarian cancers. That is not</p> <p>21 what Dr. Karageorgi studied here. He</p> <p>22 looked at endometrial cancer risk.</p> <p>23 I believe here, and I'd have</p> <p>24 to look, but I see it now. In the</p>	<p>1 results were at the low level of</p> <p>2 talc exposure and resulted in no</p> <p>3 significant increases; therefore,</p> <p>4 you didn't get a time-dependent or</p> <p>5 dose-dependent increase --</p> <p>6 BY MR. SMITH:</p> <p>7 Q. Well, I don't want to go</p> <p>8 back over it --</p> <p>9 A. -- in gene expression.</p> <p>10 Q. -- but you don't know if you</p> <p>11 got a time or dose-dependent at the</p> <p>12 higher concentrations because you didn't</p> <p>13 test it.</p> <p>14 A. It doesn't make a</p> <p>15 difference.</p> <p>16 Q. You didn't test it at 24</p> <p>17 hours, did you?</p> <p>18 MR. FROST: Objection.</p> <p>19 BY MR. SMITH:</p> <p>20 Q. Did you? Yes or no?</p> <p>21 MR. FROST: Objection.</p> <p>22 THE WITNESS: Low</p> <p>23 concentrations, yes, we did.</p> <p>24 BY MR. SMITH:</p>
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<p>1 abstract, it was a borderline increase in</p> <p>2 risk, and it was not related to dose or</p> <p>3 frequency. And he concludes that future</p> <p>4 studies need to be done to make</p> <p>5 conclusions.</p> <p>6 Q. On Page 30, on the -- one,</p> <p>7 two, three, four -- fourth bullet point,</p> <p>8 starting "On Page 12," of your report.</p> <p>9 It says, "On page 12." It goes down and</p> <p>10 says, "He does not acknowledge that ATF3</p> <p>11 was characterized as an inhibitor of</p> <p>12 inflammation in our studies, and unlike</p> <p>13 asbestos, no changes in gene expression</p> <p>14 were observed at 24 hours in mesothelial</p> <p>15 or ovarian epithelial after exposure to</p> <p>16 talc."</p> <p>17 That is not true. They were</p> <p>18 not done at 24 at high concentrations,</p> <p>19 were they?</p> <p>20 MR. FROST: Objection.</p> <p>21 BY MR. SMITH:</p> <p>22 Q. Were they?</p> <p>23 MR. FROST: Objection.</p> <p>24 THE WITNESS: The 24-hour</p>	<p>1 Q. High concentration. The</p> <p>2 higher concentration, did you?</p> <p>3 MR. FROST: Objection.</p> <p>4 THE WITNESS: We didn't look</p> <p>5 at asbestos or talc at high</p> <p>6 concentrations.</p> <p>7 MR. FROST: How are we doing</p> <p>8 on time?</p> <p>9 THE VIDEOGRAPHER: You've</p> <p>10 got a minute left.</p> <p>11 BY MR. SMITH:</p> <p>12 Q. Okay.</p> <p>13 And you talk about</p> <p>14 Dr. Saed's lack of knowledge about</p> <p>15 ovarian cancer. Have you seen the</p> <p>16 publications that he's published on,</p> <p>17 Doctor?</p> <p>18 MR. FROST: Objection.</p> <p>19 THE WITNESS: Do you want me</p> <p>20 to answer that?</p> <p>21 Yes, the few he has which</p> <p>22 are not in high impact journals</p> <p>23 and not what they say they are.</p> <p>24 BY MR. SMITH:</p>

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<p>1 Q. Let me tell you what -- I'll 2 tell you what, I take exception to you 3 laughing and your sarcasm about Dr. Saed. 4 I just want to tell you I take -- 5 A. Well -- 6 Q. -- I think that is low rent 7 and classless. 8 But my question to you is, 9 do you know if he's published any 10 peer-reviewed literature prior to 11 litigation on oxidative stress and 12 inflammation and it leading to ovarian 13 cancer? Do you know at this time? 14 A. He's had -- 15 MR. FROST: Objection. 16 THE WITNESS: He's had a few 17 papers on chemo resistance in 18 ovarian cancer cells. 19 BY MR. SMITH: 20 Q. Have you had any prior 21 publications in that area? 22 MR. FROST: Objection. 23 BY MR. SMITH: 24 Q. Yourself?</p>	<p>1 2 CERTIFICATE 3 4 5 I HEREBY CERTIFY that the 6 witness was duly sworn by me and that the 7 deposition is a true record of the 8 testimony given by the witness. 9 10 It was requested before 11 completion of the deposition that the 12 witness, BROOKE T. MOSSMAN, M.S., Ph.D., 13 have the opportunity to read and sign the 14 deposition transcript. 15 16 MICHELLE L. GRAY, 17 A Registered Professional 18 Reporter, Certified Shorthand 19 Reporter, Certified Realtime 20 Reporter and Notary Public 21 Dated: April 9, 2019 22 23 (The foregoing certification 24 of this transcript does not apply to any reproduction of the same by any means, unless under the direct control and/or supervision of the certifying reporter.)</p>
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<p>1 A. In chemo resistance, no. 2 MR. FROST: How are we 3 doing? We done? 4 All right. Great. Let me 5 just consult with my colleague, 6 but I have a feeling we're done. 7 Yeah, we're done. 8 THE VIDEOGRAPHER: This 9 concludes today's deposition. 10 We're going off the record. The 11 time is 5:55. 12 (Excused.) 13 (Deposition concluded at 14 approximately 5:55 p.m.) 15 - - - 16 17 18 19 20 21 22 23 24</p>	<p>1 INSTRUCTIONS TO WITNESS 2 3 Please read your deposition 4 over carefully and make any necessary 5 corrections. You should state the reason 6 in the appropriate space on the errata 7 sheet for any corrections that are made. 8 After doing so, please sign 9 the errata sheet and date it. 10 You are signing same subject 11 to the changes you have noted on the 12 errata sheet, which will be attached to 13 your deposition. 14 It is imperative that you 15 return the original errata sheet to the 16 deposing attorney within thirty (30) days 17 of receipt of the deposition transcript 18 by you. If you fail to do so, the 19 deposition transcript may be deemed to be 20 accurate and may be used in court. 21 22 23 24</p>

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<div style="text-align: right; padding-right: 20px;">Page 511</div> <p>ACKNOWLEDGMENT OF DEPONENT</p> <p>I, _____, do</p> <p>hereby certify that I have read the foregoing pages, 1 - 512, and that the same is a correct transcription of the answers given by me to the questions therein propounded, except for the corrections or changes in form or substance, if any, noted in the attached Errata Sheet.</p> <p>_____</p> <p>BROOKE T. MOSSMAN, M.S., Ph.D.    DATE</p> <p>Subscribed and sworn to before me this _____ day of _____, 20____.</p> <p>My commission expires: _____</p> <p>_____</p> <p>Notary Public</p>	

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<b>2006</b> 93:2	159:20	311:10,17	<b>334</b> 2:10	216:23 288:9
218:21 220:18	<b>22</b> 226:6,20	394:13 500:10	<b>34</b> 353:6 355:3	470:19
<b>2007</b> 198:1	227:3,6	502:16	409:23 413:6	<b>463</b> 10:15
336:2 345:19	<b>222</b> 7:15	<b>299</b> 8:6	<b>346</b> 8:21	<b>463-2400</b> 3:14
<b>2008</b> 236:13	<b>226</b> 7:11	<b>2A</b> 419:19	<b>35</b> 192:9,13	<b>465</b> 10:17
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<b>2009</b> 235:9	<b>24</b> 47:20 48:14	<b>3</b> 16:16 59:1,15	<b>36</b> 412:12	
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# Exhibit U

# Pycnogenol® reduces Talc-induced Neoplastic Transformation in Human Ovarian Cell Cultures

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Talc and poor diet have been suggested to increase the risk of developing ovarian cancer; which can be reduced by a diet rich in fruit and vegetables. Talc is ubiquitous despite concern about its safety, role as a possible carcinogen and known ability to cause irritation and inflammation. It was recently shown that Pycnogenol® (Pyc; a proprietary mixture of water-soluble bioflavonoids extracted from French maritime pine bark) was selectively toxic to established malignant ovarian germ cells. This study investigated talc-induced carcinogenesis and Pyc-induced chemoprevention. Normal human epithelial and granulosa ovarian cell lines and polymorphonuclear neutrophils (PMN) were treated with talc, or pretreated with Pyc then talc. Cell viability, reactive oxygen species (ROS) generation and neoplastic transformation by soft agar assay were measured. Talc increased proliferation, induced neoplastic transformation and increased ROS generation time-dependently in the ovarian cells and dose-dependently in the PMN. Pretreatment with Pyc inhibited the talc-induced increase in proliferation, decreased the number of transformed colonies and decreased the ROS generation in the ovarian cells. The data suggest that talc may contribute to ovarian neoplastic transformation and Pyc reduced the talc-induced transformation. Taken together, Pyc may prove to be a potent chemopreventative agent against ovarian carcinogenesis. Copyright © 2007 John Wiley & Sons, Ltd.

**Keywords:** ovarian cancer; talc; Pycnogenol®; human neutrophils.

## INTRODUCTION

Ovarian cancer is the sixth most commonly occurring cancer and ranks fifth in cancer deaths among women, accounting for more deaths than any other cancer of the female reproductive system. Epidemiological studies have suggested that diet, talc, industrial pollutants, smoking, asbestos and infectious agents may increase the risk of developing ovarian cancer (American Cancer Society, 2000) and may do so by causing localized inflammation (Ness and Cottreau, 1999). Specifically, talc exposure has been cited as a risk factor because of its similarity to asbestos (Cramer *et al.*, 1999).

Talc is a layered magnesium silicate [ $\text{Mg}_3\text{Si}_4\text{O}_{10}(\text{OH})_2$ ]. It is used in cosmetics (as the primary ingredient in talcum powder), pharmaceuticals (as an excipient in tablets) and in many other industrial applications (Bremmell and Addai-Mensah, 2005). Talc is used medically to induce pleurodesis because of its known ability to cause irritation and inflammation (Holthouse and Chleboun, 2001). Animal studies showed a systemic migration of talc particles to various organs despite route of entry (Henderson *et al.*, 1986; Werebe *et al.*, 1999). Exposure of rat ovaries to talc leads to cyst formation (Hamilton *et al.*, 1984). Talc was also shown to cause superoxide anion generation and release from murine macrophages (Van Dyke *et al.*, 2003). Thus controversy

continues to surround the topic of talc, its safety (Janssen, 2004) and its role as a possible carcinogen (Cramer *et al.*, 1999; Wong *et al.*, 1999).

Lifestyle factors are important in the etiology of ovarian cancer and current evidence suggests the risk can be reduced by eating a diet rich in fruit and vegetables, among other lifestyle choices (Hanna and Adams, 2006). For the past 20 years, researchers have proposed that nutritional factors play one of the most important roles in the etiology of human cancer. It is estimated that 35% (range 10–70%) of all cancers are diet related and that consumption of certain fruits and vegetables is inversely associated with the incidence of specific forms of cancer. Past research has indicated that a large number of bioactive components, which proved to be protective on different stages of cancer formation, have been identified in nutrients that are of plant origin (Knasmüller and Verhagen, 2002).

Pycnogenol® (Pyc) is a proprietary mixture of water-soluble bioflavonoids extracted from the bark of French maritime pine (*Pinus maritima* Aiton; currently known as *Pinus pinaster* Aiton). The main constituents of Pyc are phenolic compounds, broadly divided into monomers (catechin, epicatechin and taxifolin) and condensed flavonoids (classified as procyanidins and proanthocyanidins). Pyc is known to possess potent antioxidant activity, it not only scavenges the free radicals but it also enhances the endogenous antioxidant systems (Nelson *et al.*, 1998; Wei *et al.*, 1997). Pyc has also been shown to selectively induce apoptosis in breast cancer cells (Huyhn and Teel, 2000) and induce differentiation and apoptosis in human promyeloid leukemia cells (Huang *et al.*, 2005). It was previously

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shown that Pyc selectively induced cell death in established malignant ovarian germ cells *in vitro* (Buz'Zard and Lau, 2004). This study now reports that Pyc prevents talc-induced neoplastic transformation of normal ovarian cells, *in vitro*.

## MATERIALS AND METHODS

**Reagents and chemicals.** Pycnogenol® was supplied by Horphag Research (Geneva, Switzerland). Talc, crystal violet, Giemsa stain, RPMI-1640 medium and other miscellaneous chemicals were purchased from Sigma (St Louis, MO). Polymorphoprep™ was purchased from Greiner Bio-One, Inc. (Longwood, FL). Dulbecco's modification of Eagle's Medium (DMEM), Ham's F-12 medium and penicillin–streptomycin (P-S) were purchased from Cellgro (Herndon, VA). Fetal bovine serum (FBS) was purchased from HyClone (Logan, UT). The CellTiter 96® AQueous One Solution Cell Proliferation Assay was purchased from Promega (Madison, WI). High strength analytical grade agarose was purchased from Bio-Rad (Hercules, CA). Ionagar No. 2 was purchased from Oxoid (London, UK). 5-(and-6)-Carboxy-2',7'-dichlorodihydrofluorescein diacetate (carboxy-H<sub>2</sub>DCFDA) was purchased from Molecular Probes (Carlsbad, CA).

**Water soluble extraction of Pycnogenol®.** Pyc was incubated at 56 °C for 5 h in double distilled water, allowed to cool to room temperature and filtered using a Steriflip® Vacuum Filtration System (0.22 µm Durapore PVDF membrane; Millipore Corporation, Bedford, MA).

**Cell culture and treatments.** Two cell cultures of human origin were maintained at 37 °C in a humidified atmosphere containing 5% CO<sub>2</sub>. OSE2a (immortalized normal ovarian epithelial) and GC1a (immortalized normal ovarian granulosa) cell cultures were donated by Dr Hitoshi Okamura at Kumamoto University, Japan (Okamura *et al.*, 2003). The cell lines were maintained in a 1:1 mixture of DMEM and Ham's F-12 medium supplemented with 10% FBS and 100 IU/mL P-S. In preparation for either talc or Pyc + talc treatments, each cell line was seeded ( $1 \times 10^5$  cells/ml) and grown to 80% confluence, unless otherwise specified. Cells were incubated with 0–500 µg/mL talc from 24 to 120 h; or 0–500 µg/mL Pyc for 24 h followed by 5 µg/mL talc for 24 or 72 h.

**Neutrophil isolation and culture.** Peripheral blood polymorphonuclear neutrophils (PMN) and monocytes were obtained from heparinized venous blood from healthy volunteers (protocol approved by Loma Linda University Institutional Review Board for Human Studies) and isolated by Polymorphoprep™ density gradient centrifugation followed by the hypotonic lysis of erythrocytes. The purity of PMNs was determined by Giemsa staining as greater than 95%. Purified cells were suspended at  $5 \times 10^5$  cells/mL in RPMI-1640 containing 2 mM L-glutamine, 1 mM sodium pyruvate, supplemented with 10% FBS and 100 IU/mL P-S; and treated with varying concentrations of talc for 24 or 72 h. ROS generation was detected as detailed below.

**Cell viability assay.** The CellTiter 96® AQueous One Solution Cell Proliferation Assay was used to measure cell viability (Buz'Zard and Lau, 2004). The MTS [3-(4,5-dimethylthiazolyl-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulphophenyl)-2H-tetrazolium, inner salt] solution was used according to manufacturer's instructions. The absorbance was read at 490 nm using a model 3550 Microplate Reader (Bio-Rad). The percent cell viability was calculated as the absorbance of the treated cells divided by the absorbance of the untreated-control cells multiplied by 100.

**Neoplastic transformation assay.** A characteristic of cancer cells is their ability to grow and to divide when held in suspension without attachment or with minimal attachment to a rigid surface (Leung *et al.*, 2004). Thus, growth in soft agar demonstrates *in vitro* transformation of cells to their neoplastic counterparts (Morales *et al.*, 2003). After 72 h of incubation in the presence of talc; or in the presence of 0–500 µg/mL Pyc for 24 h followed by 5 µg/mL talc for 72 h, cells were collected, washed and suspended in 0.35% agarose at 5000 cells/well and layered on top of a base of 0.5% agar. The plates were incubated at 37 °C in a humidified incubator for 14 days. The cells were stained with 0.005% crystal violet and colonies were counted using an inverted microscope (Cory *et al.*, 1987).

**Reactive oxygen species (ROS) detection.** Carboxy-H<sub>2</sub>DCFDA is a non-fluorescent dye that permeates the cells where it is deacetylated by viable cells to 2',7'-dichlorofluorescein (DCFH), which is then oxidized to fluorescent 2',7'-dichlorofluorescein (DCF) by endogenous hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) (Wan *et al.*, 1993). The cells were seeded in Optilux™ 96-well plates (BD Falcon, Bedford, MA) and treated with 0 to 500 µg/mL Pyc for 24 h. H<sub>2</sub>O<sub>2</sub> (100 µM) was used as a positive control. Carboxy-H<sub>2</sub>DCFDA (5 µM) was added and incubated for 1 h. The fluorescence intensity (excitation 485 nm/emission 530 nm) was measured as arbitrary fluorescent units (AFU) using a model 7600 Microplate Fluorometer (Cambridge Technology, Inc., Watertown, MA). The percent AFU (a.k.a. % ROS generation) was calculated as the 'treated cell-AFU' divided by the 'untreated cell-AFU' multiplied by 100. Immediately following the fluorescence detection, the fluorescence intensity was normalized by the cell viability assay.

**Statistical analysis.** Data were reported as mean ± SE. Statistical analysis was performed with the Student's paired *t*-test.

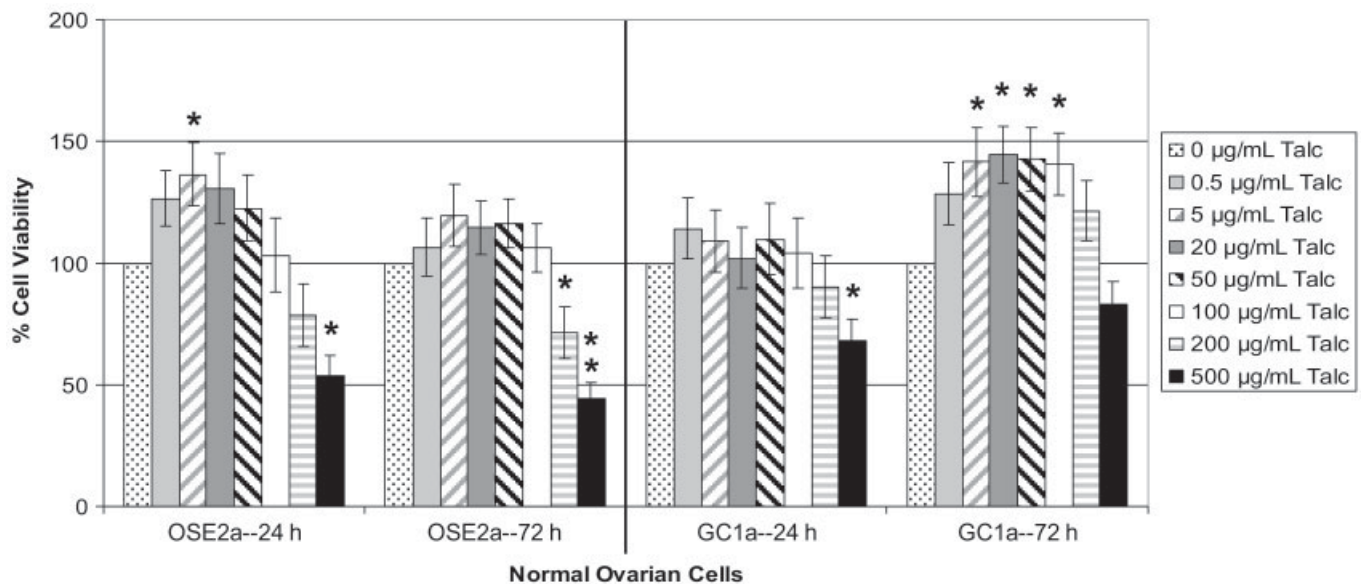
## RESULTS

All experiments were performed a minimum of three times with reproducible results.

### Effect of talc on cell viability of normal ovarian cells

Talc caused a bell-shaped curve response in OSE2a cells, with a statistically significant increase seen at 5 µg/mL (24 h) and a statistically significant decrease at 200 µg/mL (72 h) and 500 µg/mL (24 and 72 h) (Fig. 1).





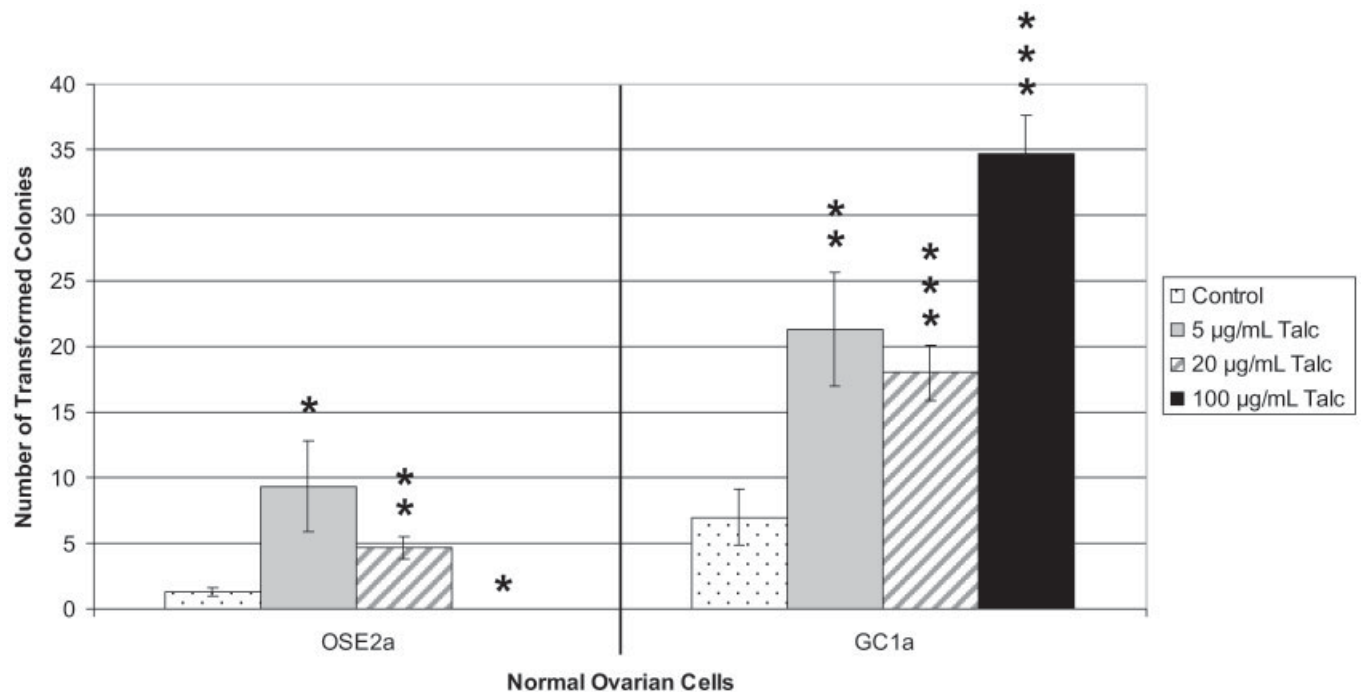
**Figure 1.** Effect of talc on the cell viability of ovarian cells. Normal ovarian epithelial (OSE2a) and normal ovarian stromal (GC1a) cells were treated with various concentrations of talc for 24 and 72 h. Cell viability was measured by the MTS assay and the percent cell viability was calculated as the absorbance of the treated cell divided by the absorbance of the untreated-control cells multiplied by 100. Each data point represents mean  $\pm$  SE of five determinations. Statistical significance was determined by the Student's paired *t*-test. \*  $p < 0.05$ , \*\*  $p < 0.01$  comparing the treatment with the respective untreated control.

Also seen in Fig. 1, talc caused a bell-shaped curve response in GC1a cells, with a statistically significant increase seen at 5, 20, 50 and 100  $\mu\text{g/mL}$  (72 h) and a statistically significant decrease at 500  $\mu\text{g/mL}$  (24 h).

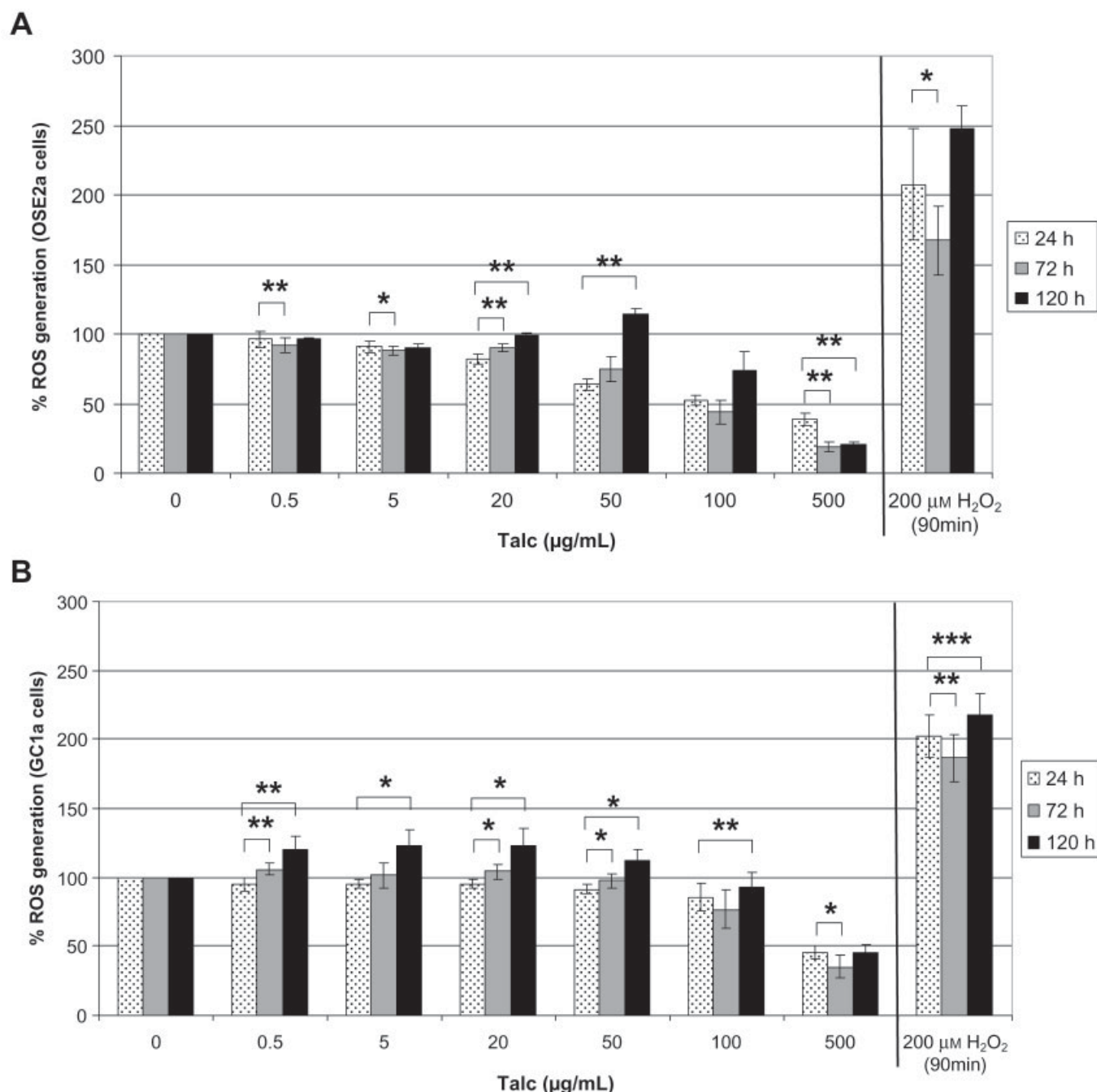
#### Effect of talc on neoplastic transformation of normal ovarian cells

Since the ability to grow suspended in soft agar is a characteristic of cells being transformed to their

neoplastic counterparts (Leung *et al.*, 2004; Morales *et al.*, 2003), the study determined whether talc would be able to induce such a transformation. As shown in Fig. 2, talc caused a statistically significant increase in the number of transformed colonies in the OSE2a cells at 5 and 20  $\mu\text{g/mL}$  talc and in the GC1a cells at 5, 20 and 100  $\mu\text{g/mL}$  talc, compared with the untreated control. An exception was seen in the 100  $\mu\text{g/mL}$  talc treatment in the OSE2a cells in which the number of transformed colonies was reduced significantly.



**Figure 2.** Neoplastic transformation of ovarian cells by talc. Normal ovarian epithelial (OSE2a) and normal ovarian stromal (GC1a) cells were incubated with various concentrations of talc for 72 h, collected, washed, seeded in soft agar suspension and grown for 14 days before colonies were counted. Each data point represents mean  $\pm$  SE of three determinations. Statistical significance was determined by the Student's paired *t*-test. \*  $p < 0.05$ , \*\*  $p < 0.01$  and \*\*\*  $p < 0.001$  comparing the treatment with the respective untreated control (0  $\mu\text{g/mL}$  talc).



**Figure 3.** ROS generation of ovarian cells in response to talc treatments. Normal ovarian epithelial (OSE2a) and normal ovarian stromal (GC1a) cells were treated with various concentrations of talc for 24, 72 and 120 h and H<sub>2</sub>O<sub>2</sub> during the last 90 min of each respective time point. H<sub>2</sub>O<sub>2</sub> was used as a positive control for this assay. Fluorescence intensity were measured as arbitrary fluorescent units (AFU) at ex 485 nm/em 530 nm and normalized with the cell viability assay. Percent AFU (a.k.a. % ROS generation) was calculated as the average AFU of the treated cell divided by the average AFU of the untreated-control cells multiplied by 100. (A) ROS generation in OSE2a cells in response to talc treatments. (B) ROS generation in GC1a cells in response to talc treatments. Each data point represents mean  $\pm$  SE of three determinations. Statistical significance was determined by the Student's paired *t*-test. \*  $p < 0.05$ , \*\*  $p < 0.01$  and \*\*\*  $p < 0.001$  comparing the treatment with the respective untreated control (as demonstrated by the horizontal brackets).

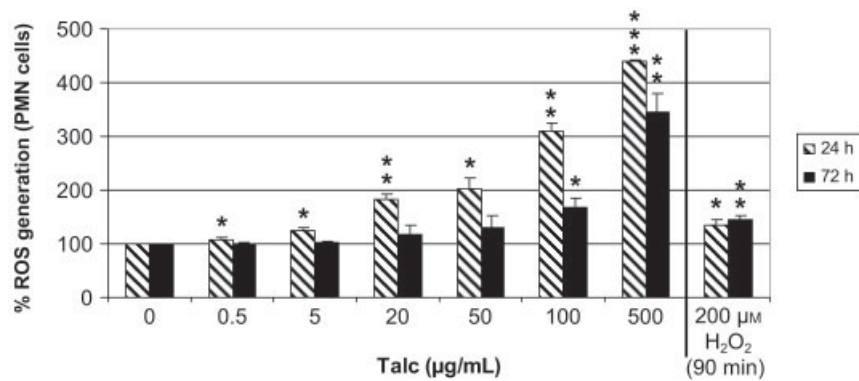
#### Effect of talc on ROS generation in normal ovarian cells

Talc caused an initial dose-dependent decrease in ROS generation (24 h) which increased with time in OSE2a cells (Fig. 3A). However, as time increased, ROS generation rebounded and increased compared with the values at 24 h. A statistically significant increase was seen at 20 µg/mL (72 and 120 h) and 50 µg/mL (120 h). Talc also caused an initial dose-dependent decrease in ROS generation (24 h) in GC1a cells (Fig. 3B), but

ROS generation increased with time in the talc treated cells. A statistically significant increase was seen with 0.5, 20 and 50 µg/mL (72 and 120 h), as well as 5 and 100 µg/mL (120 h) compared with the respective 24 h value.

#### Effect of talc on ROS generation in PMN

Since oxidative stress is often a component of the tumor microenvironment (Valko *et al.*, 2004), the study tested whether talc was capable of inducing ROS generation



**Figure 4.** ROS generation of polymorphonuclear neutrophils (PMN) in response to talc treatments. PMNs were treated with various concentrations of talc for 24 and 72 h and H<sub>2</sub>O<sub>2</sub> during the last 90 min of each respective time point. H<sub>2</sub>O<sub>2</sub> was used as a positive control for this assay. Fluorescence intensity were measured as arbitrary fluorescent units (AFU) at ex 485 nm/em 530 nm and normalized with the cell viability assay. Percent AFU (a.k.a. % ROS generation) was calculated as the average AFU of the treated cell divided by the average AFU of the untreated-control cells multiplied by 100. ROS generation of PMNs in response to talc treatments. Each data point represents mean  $\pm$  SE of three determinations. Statistical significance was determined by the Student's paired *t*-test. \*  $p < 0.05$ , \*\*  $p < 0.01$  and \*\*\*  $p < 0.001$  comparing the treatment with the respective untreated control.

in human PMNs. Talc caused a dose-dependent increase in ROS generation at both time points (Fig. 4). The increase was statistically significant at 0.5, 5, 20, 50  $\mu$ g/mL (24 h) and 100 and 500  $\mu$ g/mL (24 and 72 h). The maximum ROS generation was seen at 500  $\mu$ g/mL and was increased over 4-fold at 24 h and 3.5-fold at 72 h, compared with the respective untreated cells.

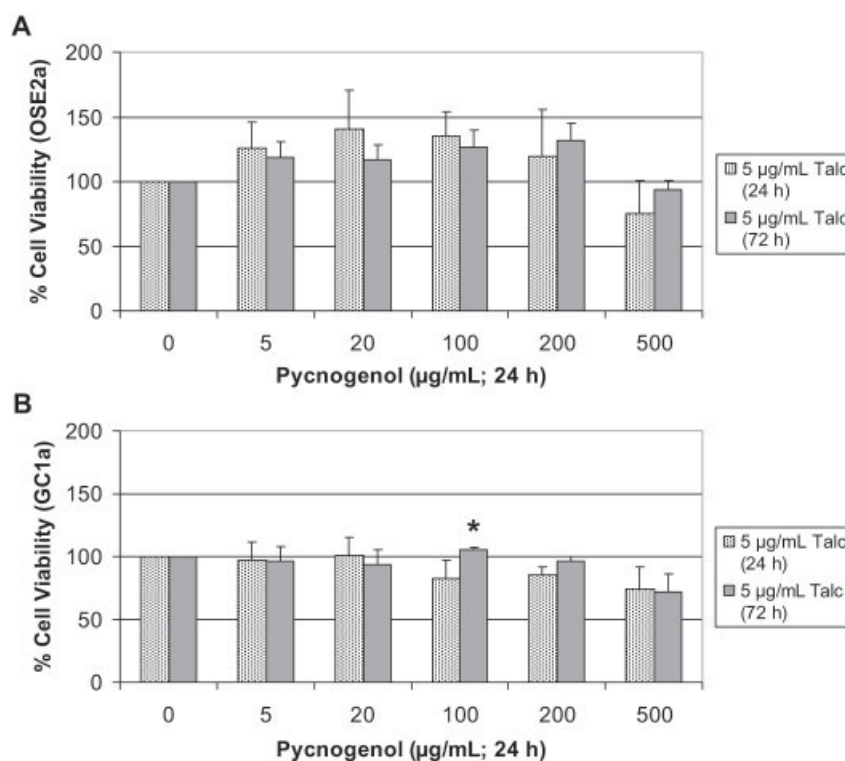
(Fig. 5A). Pretreatment with Pyc caused a general decrease in cell viability in the GC1a cells (Fig. 5B) compared with the respective untreated GC1a cells. One exception is that of a slight, but statistically significant, increase in cell viability at 100  $\mu$ g/mL Pyc + 5  $\mu$ g/mL talc (72 h) compared with the respective untreated GC1a cells (Fig. 5B).

#### Effect of pretreatment with Pyc on talc-induced cell viability changes in normal ovarian cells

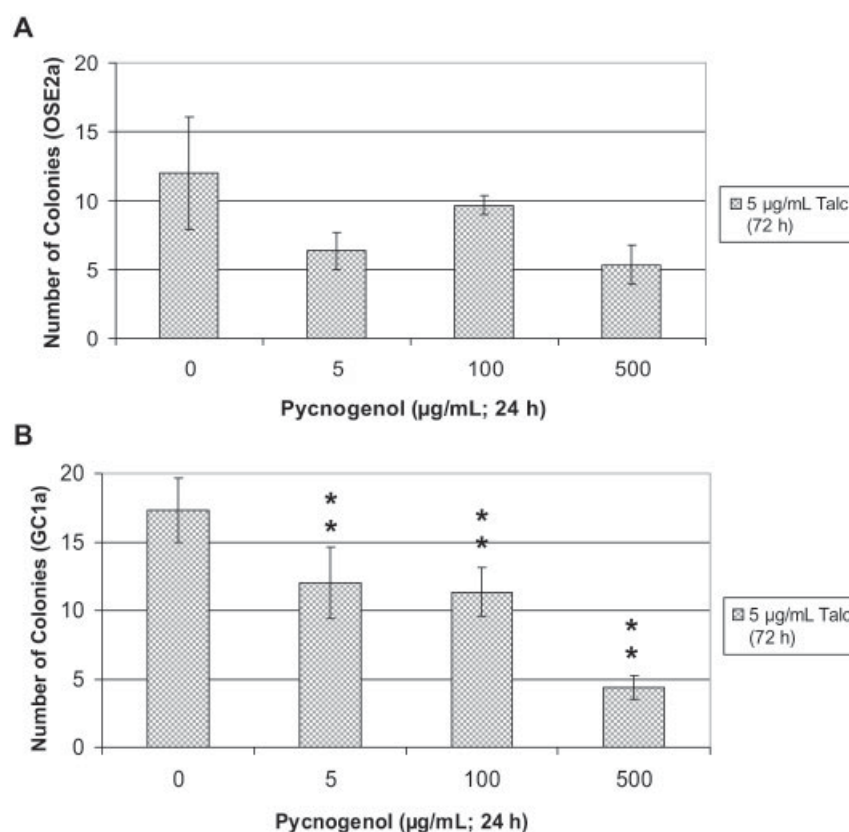
Pretreatment with Pyc did not cause a statistically different change in cell viability in the OSE2a cells

#### Effect of pretreatment with Pyc on talc-induced neoplastic transformation of normal ovarian cells

Pretreatment with Pyc decreased the number of neoplastically transformed colonies induced by talc in



**Figure 5.** Effect of Pyc + talc treatments on the cell viability of ovarian cells. Normal ovarian epithelial (OSE2a) and stromal (GC1a) cells were treated with 0–500  $\mu$ g/mL Pyc for 24 h followed by 5  $\mu$ g/mL talc for 24 and 72 h. Cell viability was measured by the MTS assay and percent cell viability was calculated as the absorbance of the treated cell divided by the absorbance of the untreated-control cells multiplied by 100. (A) OSE2a cells. (B) GC1a cells. Each data represent mean  $\pm$  SE of four determinations. Statistical significance was determined by the Student's paired *t*-test. \*  $p < 0.05$  comparing the treatment with the respective untreated control.



**Figure 6.** Pyc-induced protection against neoplastic transformation of ovarian cells by talc. Normal ovarian epithelial (OSE2a) and stromal (GC1a) cells were incubated with 0–500 μg/mL Pyc for 24 h followed by 5 μg/mL talc for 72 h, collected, washed, seeded in soft agar suspension and grown for 14 days before colonies were counted. (A) OSE2a cells. (B) GC1a cells. Each data represent mean  $\pm$  SE of three determinations. Statistical significance was determined by the Student's paired *t*-test. \*\*  $p < 0.01$  comparing the treatment with the respective control.

the OSE2a cells, but not in a statistically significant manner (Fig. 6A). Pretreatment with Pyc (5, 100 and 500 μg/mL; 24 h) caused a statistically significant decrease in the number of talc-induced neoplastically transformed colonies in the GC1a cells (Fig. 6B).

#### Effect of pretreatment with Pyc on talc-induced ROS generation in normal ovarian cells

Pretreatment with Pyc caused a statistically significant decrease in ROS generation at 5, 20, 50, 100 and 200 μg/mL Pyc + 5 μg/mL talc (24 h); and 500 μg/mL Pyc + 5 μg/mL talc (24 and 72 h) in the OSE2a cells (Fig. 7A). Pretreatment with Pyc caused a statistically significant decrease in ROS generation at 5, 20, 50, 200 and 500 μg/mL Pyc + 5 μg/mL talc (24 h) in the GC1a cells (Fig. 7B). Pretreatment with Pyc caused a statistically significant decrease in ROS generation at 5, 20, 50, 100, 200 and 500 μg/mL Pyc + 5 μg/mL talc (72 h) in the GC1a cells (Fig. 7B). The decrease seen at 100 μg/mL Pyc + 5 μg/mL talc (24 h) was not statistically significant (Fig. 7B).

#### DISCUSSION

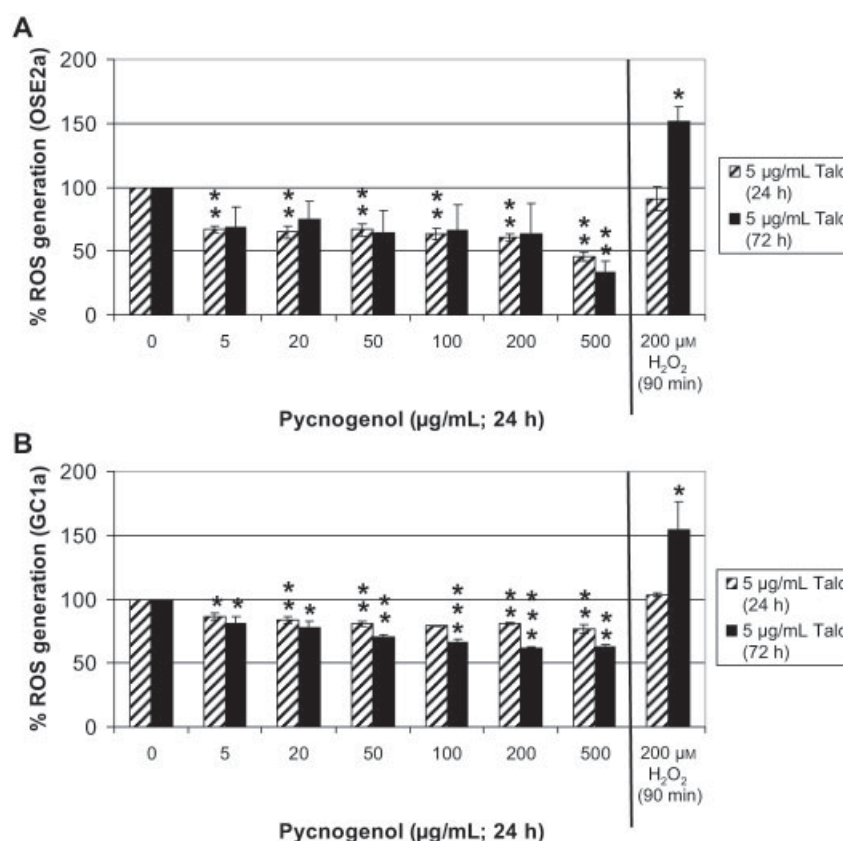
Cancer development is a multi-step process comprising a series of cellular and molecular changes that are mediated by various endogenous and exogenous stimuli, such as aberrantly expressed ROS (Storz, 2005).

Although ROS are a byproduct of endogenous biochemical processes, ROS (such as  $H_2O_2$ ) at high concentrations or expressed in a chronic nature can damage cellular macromolecules and contribute to neoplastic transformation and tumor growth (Nicco *et al.*, 2005). A characteristic of neoplastically transformed cells is their ability to grow and to divide when held in suspension without attachment or with minimal attachment to a rigid surface (Leung *et al.*, 2004; Morales *et al.*, 2003). Our data show that talc not only increased cell viability (Fig. 1A), but also caused an increase in transformed cells in both the stromal and epithelial ovarian cells by their ability to grow, divide and form colonies while being suspended in soft agar (Fig. 2A).

It is known that substances that raise the intracellular level of  $H_2O_2$  are able to trigger normal cell proliferation and abolish tumor cell proliferation (Ness and Cottreau, 1999; Nicco *et al.*, 2005). In normal cells, the basal level of  $H_2O_2$  is low and its increase is initially associated with cell growth.  $H_2O_2$  at high concentrations or expressed in a chronic nature in normal cells, can damage cellular macromolecules and contribute to neoplastic transformation and tumor growth (Nicco *et al.*, 2005). In this study, talc was shown to increase the ROS generation, after an initial suppression, in a time-dependent manner in the normal stromal cells (Fig. 3B) and less strongly in the normal epithelial cells (Fig. 3A).

Recent studies have expanded the concept that inflammation is a critical component of tumor progression. The neoplastic process (proliferation, survival and





**Figure 7.** ROS generation of ovarian cells in response to Pyc + talc. Normal ovarian epithelial (OSE2a) and stromal (GC1a) cells were treated with 0–500 µg/mL Pyc for 24 h, followed by 5 µg/mL talc for 24 or 72 h and H<sub>2</sub>O<sub>2</sub> (the last 90 min of each time point) as a positive control. Fluorescence intensity (AFU) was measured at ex 485 nm/em 530 nm and normalized by cell viability assay. The percent ROS generation was calculated as the average AFU of treated divided by AFU of untreated-control multiplied by 100. (A) OSE2a cells. (B) GC1a cells. Each data point represents mean ± SE of three determinations. Statistical significance was determined by the Student's paired *t*-test. \* *p* < 0.05, \*\* *p* < 0.01 and \*\*\* *p* < 0.001 comparing the treatment with the respective untreated control.

migration) is linked with the tumor microenvironment and synchronized with inflammatory cells (Valko *et al.*, 2004). Polymorphonuclear neutrophils and macrophages are a main source of exogenous ROS in that they release large quantities of ROS in response to a variety of stimuli. This exogenously produced ROS is crucial in the innate immune system of the host for killing invading bacteria but may also be responsible for tissue injury, when expressed excessively or inappropriately (Lewis and Pollard, 2006). Inflammatory cells are prominent in the stromal compartment of virtually all types of malignancy. These highly versatile cells respond to the presence of stimuli in different parts of tumors (Balkwill and Mantovani, 2001). In an *in vitro* study of rat cells, both macrophages and neutrophils were found to be mutagenic in response to alpha-quartz dust, talc and diesel soot; however, neutrophils appeared to have a greater mutagenic effect (Driscoll *et al.*, 1997). This study found that talc not only increased the ROS generation in the ovarian cells (Fig. 3), but also increased the expression of ROS by the neutrophils (Fig. 4).

Talc has been shown to be ubiquitous in our modern environment (Bremmell and Addai-Mensah, 2005) despite concerns raised about its safety (Janssen, 2004), its role as a possible carcinogen (Cramer *et al.*, 1999; Wong *et al.*, 1999), and its known ability to cause irritation and inflammation (Holthouse and Chleboun, 2001). The data show that talc is capable of increasing

cell proliferation, inducing neoplastic transformation of both the normal stromal and epithelial ovarian cells *in vitro*; and increasing ROS generation in these cells as well as the PMN cells.

Cancer chemoprevention is regarded as an efficient strategy to prevent cancer. The most useful cancer chemopreventive compounds will have minimal long-term toxicity, while significantly reducing tumor incidence, delaying tumor onset or preventing tumor progression (Kapadia *et al.*, 2003). It was hypothesized that Pyc, shown to induce apoptosis in various malignant cells (Huang *et al.*, 2005; Huynh and Teel, 2000), could prevent talc-induced neoplastic transformation of normal ovarian cells. It was recently shown that Pyc selectively induced cell death in established malignant ovarian germ cells *in vitro* (Buz'Zard and Lau, 2004). The present study showed that Pyc was capable of inhibiting the above mentioned talc-induced changes. Pretreatment with Pyc prevented the characteristic talc-induced increase in cell viability of GC1a cells (Fig. 5B). Pretreatment with Pyc was able to decrease the ROS generation compared with the respective controls both in a dose- and time-dependent manner (Fig. 7). The data show that pretreatment with Pyc reduced the number of talc-induced transformed colonies in both cell lines (Fig. 6). In the GC1a cells, the decrease in the number of transformed colonies was statistically significant at all concentrations of Pyc (Fig. 6B).



In conclusion, our *in vitro* data suggest that: (1) talc may contribute to ovarian carcinogenesis in humans by way of inducing aberrant ROS generation and (2) Pyc reduces talc-induced neoplastic transformation of ovarian cells. Taken together, Pyc may prove to be a chemopreventative agent against ovarian carcinogenesis.

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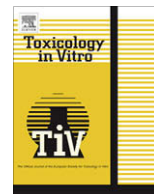
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# Exhibit V



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## Toxicology in Vitro

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# The primary role of iron-mediated lipid peroxidation in the differential cytotoxicity caused by two varieties of talc nanoparticles on A<sub>549</sub> cells and lipid peroxidation inhibitory effect exerted by ascorbic acid

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## ABSTRACT

Talc particles, the basic ingredient in different kinds of talc-based cosmetic and pharmaceutical products, pose a health risk to pulmonary and ovarian systems due to domestic and occupational exposures. Two types of talc nanoparticles depending on the source of geographical origin – indigenous- and commercial talc nanoparticles were assessed for their potential *in vitro* toxicity on A<sub>549</sub> cells; along with indigenous conventionally used microtalc particles. Cell viability, determined through live/dead staining and 3-(4,5-dimethyl thiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) assay, decreased as a function of concentration, origin and size of particles. Both varieties of talc nanoparticles differentially induced lipid peroxidation (LPO), which was correlated with the pattern of lactate dehydrogenase (LDH) leakage, reactive oxygen species (ROS) generation, and glutathione (GSH) depletion. Relatively higher cytotoxicity of indigenous nanotalc could be attributed to its higher content of iron as compared to commercial nanotalc. The known scavenger of ROS, L-ascorbic acid significantly inhibited LPO induction due to talc particles. Data suggest that nanotalc toxicity on A<sub>549</sub> cells was mediated through oxidative stress, wherein role of iron-mediated LPO was much pronounced in differential cytotoxicity.

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## 1. Introduction

Talc is a magnesium silicate mineral with chemical formula written as 3MgO·4SiO<sub>2</sub>·H<sub>2</sub>O which corresponds to 4.8% H<sub>2</sub>O, 31.7% MgO, and 63.5% SiO<sub>2</sub>. It is chemically inert to acids and alkalis and can withstand temperatures up to 1300 °C. In pulverized form it is whiter in appearance. Talc is valued for its extreme softness, smoothness, high lubricating and hiding power and ability to absorb oil and grease. Talc is, therefore, used by organized sector of industries because of its valuable properties. Pulverized talc has wide industrial applications in cosmetics as body and face powder; filler in rubber, textile, plastic, asbestos products, polishes and soaps; as a loading agent for paper of all kinds; used in pharmaceuticals as a carrier of insecticidal and pesticidal dusts.

Since, talc products are marketed in a multitude of grades which have physical or functional characteristics especially suited for particular applications and products, so occupational and con-

sumer exposures to talc are complex. Talc miners have shown higher rates of lung cancer and other respiratory illnesses from exposure to industrial grade talc, which contains dangerous silica and asbestos (Hollinger, 1990; National Toxicology Program, 1993). The common household hazard posed by talc is inhalation of baby powder by infants (Hollinger, 1990). Talc particles have been found to be translocated after intrapleural administration in rats (Werebe and Pazetti, 1999). Talc particles are able to move through the human reproductive system and become imbedded in the lining of the ovary. Researchers have found talc particles in ovarian tumors and have found that women with ovarian cancer have used talcum powder in their genital area more frequently than healthy women (Henderson et al., 1971; Harlow et al., 1992; Harlow and Hartge, 1995). Numerous studies have shown a strong link between frequent use of talc in the female genital area and ovarian cancer (Heller et al., 1996; Chang and Risch, 1997; Cook et al., 1997; Cramer et al., 1999; Mills et al., 2004; Wild, 2006). In an epidemiologic study aimed to analyze the interactions between talc use and genes involved in detoxification pathway, (viz: glutathione S-transferase M1 (GSTM1), glutathione S-transferase T1 (GSTT1), and N-acetyltransferase 2 (NAT2), suggest that women with certain genetic variants may have a higher risk of

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ovarian cancer associated with genital use of talc (Gates et al., 2008).

Nanopowder of talc is a recent introduction and is used for improving quality of many industrial products. Nanopowder of talc is being used in plastics for higher strength and stiffness, better thermal and creep resistance; in papers for higher opacity, better gloss and printing quality; in cosmetics and paints for better gloss, smoother surface, resistance to water and cracking, etc. Owing to their unique nano-size, nanoparticles are provided with many special physicochemical properties, and thereby may yield extraordinary hazards for human health (Donaldson et al., 2002; Kipen and Laskin, 2005; Holsapple et al., 2005; Nel et al., 2006; Borm et al., 2006). Since, talc with a multitude of physical and functional characteristics is used for particular applications, so occupational and consumer exposures to talc are likely to vary accordingly. Risk of occupational and environmental exposure to nanoparticles of talc has obviously increased.

Since, physical and functional characteristics of talc and other minerals depend, in part, from one geographical region/source to other, therefore, the first objective of the present study was to evaluate cytotoxicity of talc nanoparticles from the two sources-indigenous nanotalc (Indian origin) and commercial nanotalc (American origin) using human bronchoalveolar carcinoma-derived cells (A<sub>549</sub>). Indigenous micro-scale talc particle was used for comparative size-dependent toxicity with the two types of nanotalc. The second objective was to study the mechanism of cytotoxicity induced by talc nano- and micro-particles. In the present study, different types of talc particles were dispersed in the cell culture medium at varying concentrations and then exposed to cells. Cytotoxicity was measured by determining cell viability using MTT assay and live-dead staining method. To elucidate the possible mechanisms of cytotoxicity, biomarkers for cytotoxicity and oxidative stress, namely lactate dehydrogenase (LDH) leakage in cell culture medium, reactive oxygen species (ROS) generation, intracellular reduced glutathione (GSH) level, and malondialdehyde (MDA) as an indicator of lipid peroxidation and membrane damage, were measured. Antioxidant, ascorbic acid, was used to delineate further the potential mechanism of oxidative stress and as a potential preventive measure. In the toxicity of minerals, the iron content has been a key factor, acting through Fenton reaction and the Haber–Weiss cycle. Some metals like Fe, Pb, and Cr was measured in the talc from two sources. A role of differential amount of iron present in indigenous and commercial talc, in the perspective of cytotoxicity and oxidative stress has, therefore, also been established.

## 2. Materials and methods

### 2.1. Nanoparticles

Indigenous cosmetic grade talc was collected from Udaipur, Rajasthan, India and prepared into micro- and nanoparticles. As a standard reference, Nanopowder of talc (i.e. commercial nanotalc) was purchased from (M.K. Impex Canada, Catalpa Road, Mississauga, Canada). As per the information provided by the supplier, the powder size was 70–120 nm and the country of origin was USA. For indigenous nanotalc a stone of talc was crushed into fine particles and fed into a ball mill (PM 100, Retsch, Germany) and grinded for 5 days at an alternative cycles of grinding (10 min) and halt (30 min) at 350 rpm using a mixture of different sizes of balls. The sizes of nanoparticles were measured by transmission electron microscopy (TEM) and found to be 80–130 nm. Indian talc particles (i.e. indigenous micro talc) 50–65 µm served as negative control for a comparative study on nanotoxicity of indigenous and commercial varieties of nanotalc.

### 2.2. Chemicals

Fetal bovine serum, Penicillin–streptomycin, DMEM F-12 medium, HBSS was purchased from Invitrogen Co. (Carlsbad, CA, USA). MTT [3-(4,5-dimethylthiazol-2-yl)-2,5 diphenyltetrazolium bromide], NADH, Pyruvic acid, L-ascorbic acid, glutathione reduced (GSH), o-phthalaldehyde (OPT), 2',7'-dichlorofluorescein diacetate (DCFH-DA), 1,1,3,3-tetraethoxypropane (TEP), 2-thiobarbituric acid (TBA), sodium dodecyl sulphate (SDS), Na<sub>2</sub>HPO<sub>4</sub>, NaH<sub>2</sub>PO<sub>4</sub>, were obtained from Sigma–Aldrich. Ultrapure DI-water was prepared using a Milli-Q system (Millipore, Bedford, MA, USA). All other chemicals used were of reagent grade.

### 2.3. Estimation of heavy metals in indigenous and commercial talc

Talc samples were digested in digesting mixture (HNO<sub>3</sub> and perchloric acid in a ratio of 4:1) for 24 h on hot plate in a fume hood. The digested samples were dissolved in 1% HNO<sub>3</sub> and filtered. The filtrate was used for metal analysis by atomic absorption spectroscopy (AAS). Before analysis, AAS was calibrated every time by running at least three standard concentration (1, 3 and 5 mg/L) of each metal. Values have been expressed as % metal content in talc samples.

### 2.4. Measurement of hydrodynamic size of nanotalc

These particles were suspended in complete cell culture media, ultrasonicated at 30 W for 2 min (Sonics Vibra Cell, India) and a dynamic light scattering (DLS – Malvern Instruments USA) performed for particle size distribution in culture media.

### 2.5. Cell culture and treatment with talc particles

The A<sub>549</sub> cell line has been established in permanent culture from a human lung adenocarcinoma (Lieber et al., 1976). *In vitro*, these cells are largely differentiated as alveolar epithelial cells, type II (Crouse et al., 1990). The A<sub>549</sub> cells were obtained from National Centre For Cell Science (NCCS), Pune, India. Cells were maintained in DMEM F-12 medium supplemented with 10% fetal bovine serum, 100 U/ml penicillin, and 100 µg/ml streptomycin, and grown at 37 °C in a humidified, 5% CO<sub>2</sub> incubator. For the determination of GSH, MDA, and LDH levels, A<sub>549</sub> cells were plated into 75-cm<sup>2</sup> flasks at a density of  $2.0 \times 10^6$  cells per flask in 12 ml culture medium and allowed to attach for 24 h. Then, the freshly dispersed talc nanoparticles suspensions in cell culture medium were prepared and diluted to appropriate concentrations (50, 100, and 200 µg/ml) and immediately applied to the cells in 15 ml culture medium. Cells not exposed to particles served as controls in each experiment. The selection of the 50–200 µg/ml dosage range of talc nanoparticles was based on a preliminary dose–response study (data not shown). A dosage level lower than 50 µg/ml did not result cytotoxicity significantly. The 48 h exposure time was chosen for investigation; the responses at 24-h exposure were not as pronounced as that at 48 h. Therefore, all the data presented here is that of 48 h exposure. Throughout the studies presented in this paper, we utilized a particle dose of  $20 \mu\text{g}/\text{cm}^2 = 100 \mu\text{g}/\text{ml}$ .

### 2.6. Cell viability assay

Cytotoxicity was measured by determining cell viability using MTT assay and live-dead staining method.

#### 2.6.1. MTT assay

Cell proliferation/viability was assessed by the MTT assay as first described by Mossman (1983) and later modified by Hansen et al. (1989). This assay is based on the ability of viable cells, but

not of dead cells, to reduce soluble, yellow 3-(4,5-dimethyl thiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) into insoluble, blue formazan product. Briefly, around 10,000 A<sub>549</sub> cells per well were plated in 96-well microtiter plates in a 100 µl of medium. The next day, the medium was changed and the cells were treated with talc nanoparticles at 50-, 100-, and 200 µg/ml for 48 h. After the exposure time completed, the medium was aspirated off and 100 µl MTT laden media (0.5 mg MTT/ml of media without phenol red and serum, filtered through 0.22 µm filter) added and incubated for 2 h. The reaction was stopped and formazan crystal thus formed was solubilised by mixing an equal volume of stop mix solution containing 20% SDS in 50% N,N-dimethylformamide and left overnight on a shaker. To minimize the interference in absorbance caused by previously dosed talc particles (at concentrations like 50–200 µg/ml obviously resulting in turbidity!), the plates were centrifuged at 3000 rpm for 5 min to settle down the particles and a clear 100 µl supernatant was transferred to other fresh wells of microtiter plate and then absorbance at 570 nm was taken by a microplate reader (Omega Fluostar). Following noncellular background (blank consisting of yellow MTT- and stop mix-solutions) subtraction, all data were normalized to the MTT conversion activity of media-treated control cells. This value corresponds to 0% decrease in MTT conversion activity and represents 100% cell viability.

#### 2.6.2. Live-dead staining (trypan blue exclusion) assay

In addition to the MTT assay, the cell viability was also determined by the trypan blue exclusion method. The percentage of non-stained live cells was evaluated using a haemocytometer. A total of 200 cells were counted for each measurement.

#### 2.7. LDH leakage

The activity of cytoplasmic LDH released into the culture media was determined with the method described elsewhere (Wroblewski and LaDue, 1955; Welder et al., 1991). A 100-µl sample from the centrifuged culture media was collected after the cells were treated for 48 h. The LDH activity was assayed in 3.0 ml of reaction mixture with 100 µl of pyruvic acid (2.5 mg/ml phosphate buffer) and 100 µl of NADH (2.5 mg/ml phosphate buffer) and the rest of the volume adjusted with phosphate buffer (0.1 M, pH 7.4). The rate of NADH oxidation was determined by following the decrease in absorbance at 340 nm for 3 min at 30 s interval at 25 °C using a spectrophotometer (Thermo-Spectronic). The amount of LDH released is represented as LDH activity (IU/L) in culture media.

#### 2.8. Intracellular ROS measurement

The generation of intracellular ROS was measured using 2',7'-dichlorofluorescein diacetate (DCFH-DA) probe (Wang and Joseph, 1999). DCFH-DA passively enters the cell where it is broken down into cell impermeable, non-fluorescent reduced dichlorofluorescein (DCFH) and diacetate by cellular esterases. Now DCFH becomes oxidized with intracellular ROS to form the highly fluorescent compound dichlorofluorescein (DCF) that may be cell permeable. Briefly, 10 mM DCFH-DA stock solution made in dimethyl sulfoxide (DMSO) was diluted in culture medium without serum or other additive to yield a 100 µM working solution. After 48 h of exposure to talc nanoparticles, the cells in the 12-well plate were washed twice with HBSS and then incubated in 1 ml working solution of DCFH-DA at 37 °C for 30 min. The cells were lysed in alkaline solution and centrifuged at 3000 rpm. A 200 µl supernatant was transferred to black 96-well plate and fluorescence was then read at 480-nm excitation and 520-nm emission using a microplate reader (Omega Fluostar). The intensity of untreated control well was assumed to be 100% and data is represented in percent of control.

#### 2.9. Determination of intracellular GSH

The cellular content of GSH was quantified by the fluorometric assay of Hissin and Hilf (1976). After exposure, cells were lysed in 20 mM Tris (pH 7.0) by repeated cycles of freeze–thaw and centrifuged at 10,000 rpm for 10 min at 4 °C. The supernatant was transferred to another tube and protein content was measured. For the determination of intracellular GSH, protein in this supernatant was precipitated at 1% perchloric acid and again centrifuged at 10,000 rpm for 5 min at 4 °C. Now 20 µl sample was mixed with 160 µl of 0.1 M phosphate-5 mM EDTA buffer, pH 8.3 and 20 µl o-phthalaldehyde (OPT, 1 mg/ml in methanol) in a black 96-well plate. After 2 h incubation at room temperature in the dark, fluorescence was measured at an emission wavelength of 460 nm and an excitation wavelength of 355 nm, along with similarly prepared standards of GSH in 1% perchloric acid. Results are expressed as nmol GSH/mg of cellular protein.

#### 2.10. Determination of thiobarbituric acid-reactive substances (TBARS)

LPO was assessed by the TBARS assay, which detects mainly malondialdehyde (MDA), an end product of the peroxidation of polyunsaturated fatty acids and related esters. TBARS was measured by slight modification of the method of Ohkawa et al. (1979). Subconfluent cells were scraped in 75-cm<sup>2</sup> flasks, washed two times by isotonic trace element-free Tris–HCl buffer (400 mM, pH 7.3). A 200-µl aliquot of cell suspension was subsequently mixed with 800 µl of LPO assay cocktail containing (0.4% (w/v) thiobarbituric acid, 0.5% (w/v) SDS, 5% (v/v) acetic acid, pH 3.5 and incubated for 60 min at 95 °C. The sample was cooled using tap water and centrifuged at 5000 rpm for 5 min. The absorbance of the supernatants was read at 532 nm against a standard curve prepared using the MDA standard (10 mM 1,1,3,3-tetramethoxypropane in 20 mM Tris–HCl, pH 7.4). Results were calculated as nmol of MDA/mg of cellular protein.

#### 2.11. Addition of L-ascorbic acid

To test the potential antioxidant effects afforded by ascorbic acid, 1.5 mM was applied to cell culture 30 min before exposure with particles. A dosage of 200 µg/ml of the two varieties of talc was then exposed for 48 h and MDA level was measured as illustrated above.

#### 2.12. Estimation of protein

The total protein concentration was measured by the Bradford method (Bradford, 1976) using a ready to use Bradford reagent (Sigma–Aldrich, USA) and bovine serum albumin as the standard.

#### 2.13. Statistics

Data were expressed as the mean ± SD from three independent experiments. One-way ANOVA and Dunnett's Multiple Comparison Test was applied using Graph Pad prism (Version 5.0) software for significance testing, using a *p* value ≤ 0.05.

### 3. Results

#### 3.1. Iron contamination in talc samples

Indigenous and commercial talc samples were analyzed for contamination of heavy metals (Fe, Pb, and Cr). The results are given in Table 1. Indigenous talc contained almost 2.3 times higher iron level in comparison to commercial talc. Pb was not in detectable



**Table 1**  
Metal contamination in talc samples.

Name of metal	% Metal content	
	Indigenous talc	Commercial talc
Fe	0.19	0.08
Cr	Not detectable	0.0046
Pd	Not detectable	Not detectable

limit in both the samples. However Cr was present in trace amount in commercial nanotalc.

### 3.2. Hydrodynamic size of talc nanoparticles in culture media

The size measured by a dynamic light scattering method was the particles hydrodynamic size, which indicates the extent of aggregation of particles in suspension. The measurements have been given in Table 2. Results show that aggregation occurred and the aggregation was not uniform.

### 3.3. The concentration-, size-, and origin-dependent cytotoxicity of talc particles

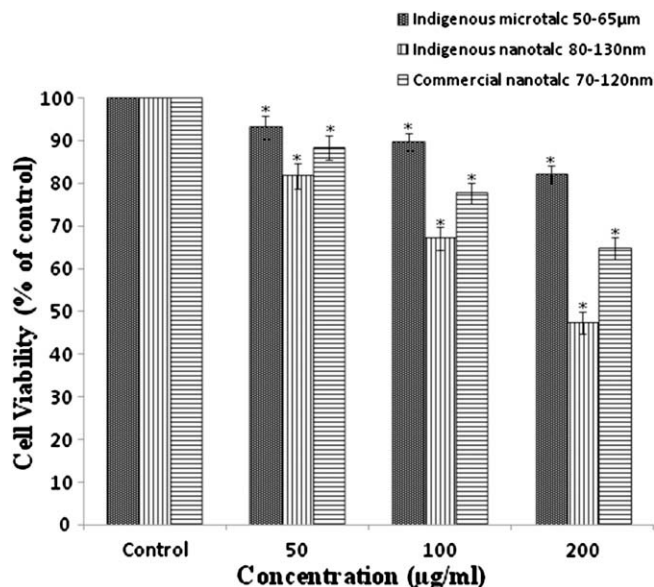
The A<sub>549</sub> cells were exposed with indigenous microtalc (50–65 µm) particles, indigenous talc nanoparticles (80–130 nm) and commercial talc nanoparticles (70–120 nm) for 48-h exposure, and the cell viability was assessed by MTT assay. Cell viability decreased as a function of concentration, size and geographical origin of particles. Cell viability decreased to 93.0%, 91.6%, and 83.6% for indigenous microtalc and 81.6%, 67.0%, and 47.30% for indigenous nanotalc and 88.3%, 77.6%, and 64.0% for commercial nanotalc particles when exposed at 50-, 100-, and 200 µg/ml, respectively (Fig. 1). Fig. 2 shows the results on cell viability obtained by trypan blue exclusion test for similar experiment. Cell viability decreased to about 93.0%, 90.6%, and 83.6% for indigenous microtalc and 83.6%, 73.6%, and 57.30% for indigenous nanotalc and 88.6%, 78.6%, and 69.6% for commercial nanotalc particles exposed at 50-, 100-, and 200 µg/ml, respectively. The IC<sub>50</sub>s evaluated by MTT and trypan blue assay is given in Table 3.

### 3.4. Cell membrane damage

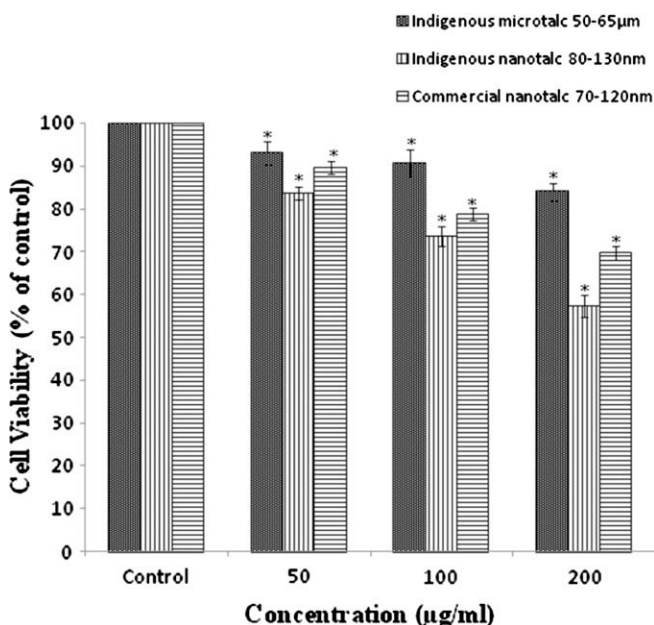
LDH release, a marker of cell membrane damage, was measured at 50, 100, and 200 µg/ml for the 48-h exposure (Fig. 3). Following exposure to talc particles at concentrations mentioned above, the LDH activity in the culture media is increased in a concentration-dependent manner and found to 18.1%, 32.9%, and 61.3%, respectively for indigenous microtalc and 99.2%, 193.6%, and 275.6%, respectively for indigenous nanotalc and 46.2%, 103.7%, and 178.7%, respectively for commercial nanotalc. The indigenous nanotalc induced a significantly higher ( $p < 0.05$ ) cell membrane damage when compared with its micro-scale size and commercial nanotalc for a particular concentration. For instance, 50-, 100-, and 200 µg/ml exposure of indigenous nanotalc induced 1.4-, 1.44-, and 1.3-fold higher membrane damage when compared with the same concentrations of commercial nanotalc induced membrane damage. Similarly indigenous nanotalc induced membrane

**Table 2**  
Actual and hydrodynamic sizes of Indigenous and Commercial nanotalc in culture media.

Type of nanoparticles	Actual size (nm)	Hydrodynamic size (nm)
Commercial nanotalc	70–120	800 ± 100
Indigenous nanotalc	80–130	750 ± 120



**Fig. 1.** Viability of A<sub>549</sub> cells after 48-h exposure to indigenous microtalc, indigenous nanotalc and commercial nanotalc particles evaluated by MTT assay at indicated concentrations. Values are mean ± SD from three independent experiments. Triplicates of each treatment group were used in each independent experiment. \*Denotes a significant difference from the control ( $p < 0.05$ ).



**Fig. 2.** Viability of A<sub>549</sub> cells after 48-h exposure to indigenous microtalc, indigenous nanotalc and commercial nanotalc particles evaluated by trypan blue assay at indicated concentrations. Values are mean ± SD from three independent experiments. Triplicates of each treatment group were used in each independent experiment. \*Denotes a significant difference from the control ( $p < 0.05$ ).

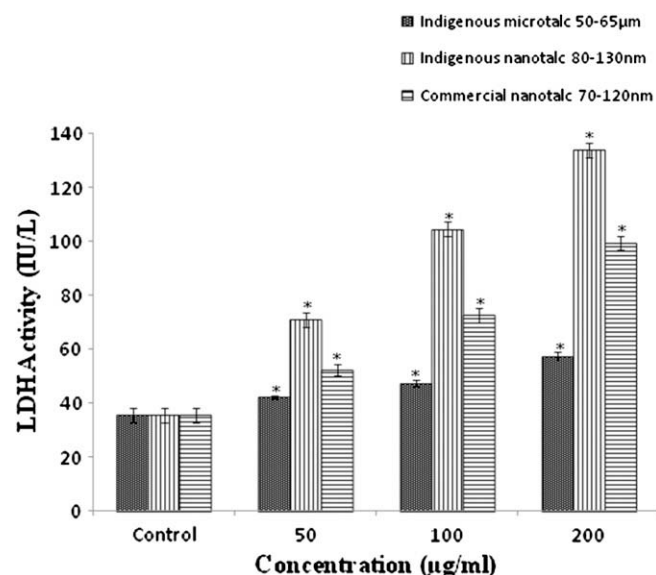
damage was 1.6-, 2.2-, and 2.3 times higher than that of indigenous microtalc.

### 3.5. ROS generation

The ability of talc micro- and nanoparticles to induce intracellular oxidant production in A<sub>549</sub> cells was assessed by measuring DCF fluorescence as a reporter of ROS generation. DCF fluorescence intensity significantly ( $p < 0.05$ ) increased after 48 h exposure to all examined micro and nanoparticles at concentrations of 50-,

**Table 3**IC<sub>50</sub> values of different talc particles measured by MTT and trypan blue.

Types of talc nanoparticles	IC <sub>50</sub> by MTT assay (μg/ml)	IC <sub>50</sub> by trypan blue assay (μg/ml)
Indigenous microtalc (50–65 μm)	600	630
Indigenous nanotalc (80–130 nm)	190	255
Commercial nanotalc (70–120 nm)	277.5	325

**Fig. 3.** The LDH activities in the cell culture medium after 48-h exposure to indigenous microtalc, indigenous nanotalc and commercial nanotalc particles at indicated concentrations. Values are mean ± SD from three independent experiments. \*Denotes a significant difference from the control ( $p < 0.05$ ).

100-, and 200 μg/ml, and evaluated to be 136%, 155%, and 175%, respectively for indigenous microtalc and 150%, 203%, and 265%, respectively for indigenous nanotalc and 136%, 175%, and 205%, respectively for commercial nanotalc (Fig. 4). The highest fluorescence obtained was that for indigenous nanotalc at 200 μg/ml.

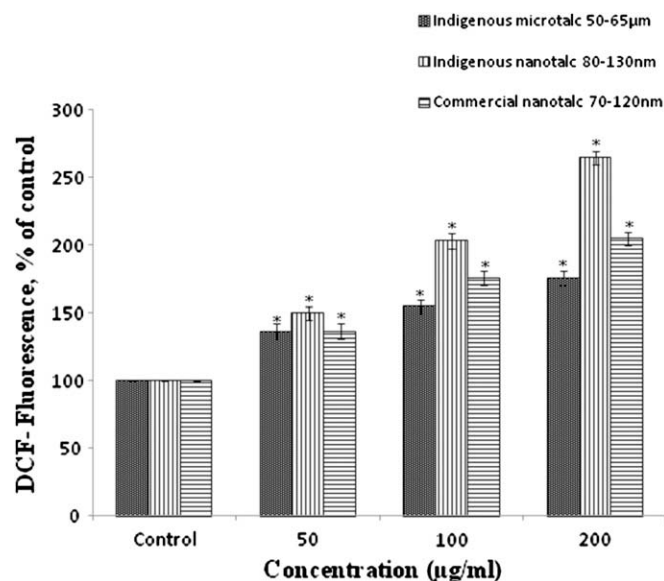
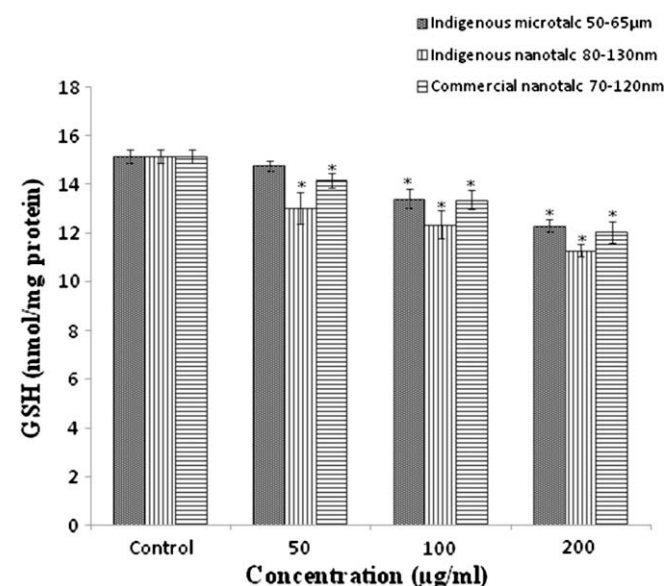
### 3.6. Cellular GSH level and LPO induced by talc nanoparticles

Following exposure to talc particles at concentrations 50, 100, and 200 μg/ml for 48 h, the intracellular GSH level exhibited a concentration-dependent decrease (Fig. 5). The GSH levels were reduced by 3%, 11.56%, and 18.8% for indigenous microtalc and 14.2%, 18.8%, and 25.4% for indigenous nanotalc and 6.6%, 11.5%, and 20.8%, respectively for commercial nanotalc.

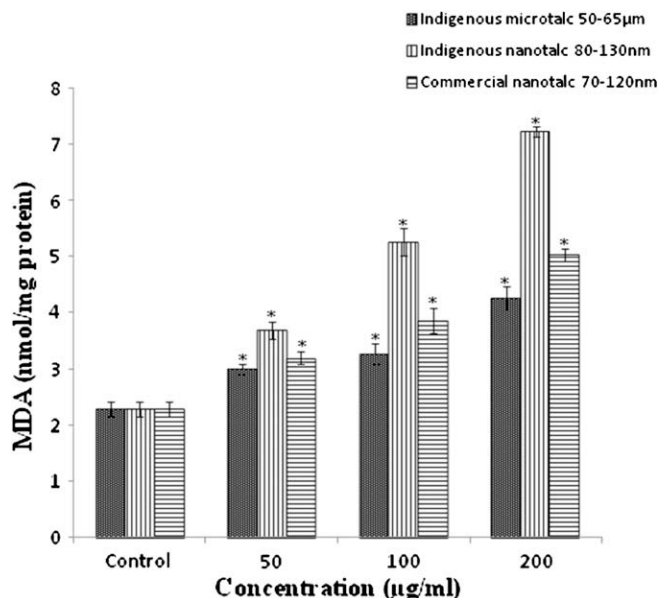
In order to elucidate the lipid peroxidation induced by talc particles, the MDA concentration was measured. Each type of nanoparticles elevated the intracellular MDA concentration which was dependent on dosage and source of talc particle origins (Fig. 6). The MDA levels were elevated by 1.3-fold, 1.4-fold, and 1.9-fold, respectively for indigenous microtalc, and 1.6-fold, 2.3-fold, and 3.1-fold, respectively for indigenous nanotalc and 1.4-fold, 1.7-fold, and 2.1-fold, respectively for commercial nanotalc, compared to the control untreated groups.

### 3.7. Inhibitory effect afforded by ascorbic acid on LPO induced by talc nanoparticles

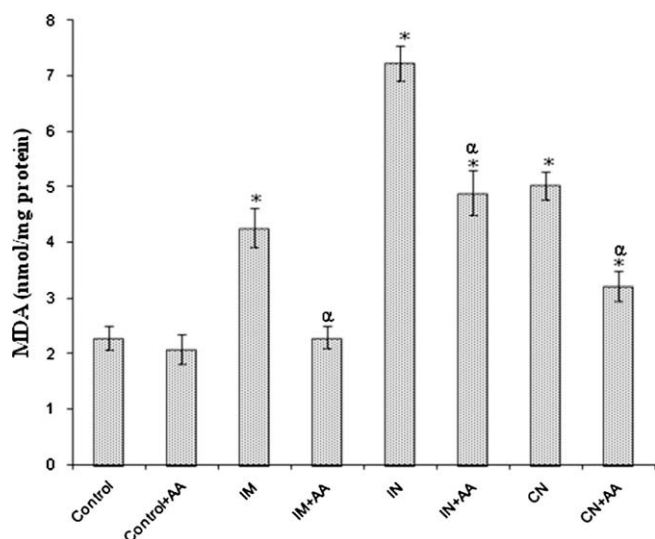
In an additional set of studies, L-ascorbic acid was added to the cells during exposure to micro- and nanotalc, each group ex-

**Fig. 4.** DCF-fluorescence intensity after 48-h exposure to indigenous microtalc, indigenous nanotalc and commercial nanotalc particles at indicated concentrations. Values are mean ± SD from three independent experiments. \*Denotes a significant difference from the control ( $p < 0.05$ ).**Fig. 5.** Cellular GSH levels of A<sub>549</sub> cells after 48-h exposure to indigenous microtalc, indigenous nanotalc and commercial nanotalc particles at indicated concentrations. Values are mean ± SD from three independent experiments. \*Denotes a significant difference from the control ( $p < 0.05$ ).

posed at 200 μg/ml, as a test to determine if the oxidative damage to A<sub>549</sub> cells could be prevented. Results show that L-ascorbic acid effectively prevented the generation of MDA level induced by talc particles (Fig. 7). MDA level was reduced up to control level for indigenous microtalc in the presence of ascorbic acid. When indigenous nanotalc induced MDA was 3.1-fold, in the presence of ascorbic acid it was reduced and found to be 2.1-fold of control. When commercial nanotalc induced MDA was 2.1-fold, in the presence of ascorbic acid it was 1.3-fold of control.



**Fig. 6.** Cellular MDA levels of A<sub>549</sub> cells after 48-h exposure to indigenous microtalc, indigenous nanotalc and commercial nanotalc particles at indicated concentrations. Values are mean  $\pm$  SD from three independent experiments. \*Denotes a significant difference from the control ( $p < 0.05$ ).



**Fig. 7.** Showing the inhibitory effect of ascorbic acid on cellular MDA levels of A<sub>549</sub> cells under indicated conditions of 48-h exposure. \*AA (1.5 mM L-ascorbic acid); IM (200 µg/ml indigenous microtalc); IN (200 µg/ml indigenous nanotalc); CN (200 µg/ml commercial nanotalc). Values are mean  $\pm$  SD from three independent experiments. \*Denotes a significant difference from the control ( $p < 0.05$ ).  $\alpha$  indicates the significant inhibitory effect of ascorbic acid (AA) on lipid peroxidation versus either, IM, IN or CN.

#### 4. Discussion

At present, an *in vitro* toxicological study of talc nanoparticles is lacking. In this study, the cytotoxicity of two types of talc nanoparticles was investigated in cultured human bronchoalveolar carcinoma-derived cells (A<sub>549</sub>). This cell line has been widely used in *in vitro* cytotoxicity studies (Huang et al., 2004; Bakand et al., 2006). Present study showed that the two types of talc nanoparticles caused significant reduction in cell viability as a function of concentration and their iron content. The talc nanoparticles from two sources induced the enhanced generation of ROS and MDA

production. Consequently, redundant free radicals would interact with biomolecules including proteins, enzymes, membrane lipids and even DNA which could be oxidized, modified, destructured and ultimately dysfunctional (Marnett, 2000; Hensley and Floyd, 2002).

Oxidative stress has been suggested to play an important role in the mechanism of toxicity of a number of compounds whether by production of free radicals or by depleting cellular antioxidant capacity. Cellular integrity is affected by oxidative stress when the production of ROS overwhelms antioxidant defense mechanism (Halliwell et al., 1992; Chen and Yu, 1994). ROS are oxygen-containing molecules, such as hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>), superoxide anion (O<sub>2</sub><sup>-</sup>), and hydroxyl radical (HO<sup>•</sup>), that have a greater chemical activity than molecular oxygen. ROS are generated in many inflammatory conditions in the lung and have been associated with cell injury and apoptosis (Anderson et al., 1994; Meyer et al., 1993). Many other studies have shown that nanoparticles may produce toxicity by generating ROS. Recently, Buz'Zard and Lau (2007) have reported enhanced ROS generation in human ovarian cell culture and have found an increased cell proliferation and neoplastic transformation of human ovarian stromal and epithelial cells exposed with talc. In the present study too, talc micro and nanoparticles induced significantly higher ROS generation compared with untreated A<sub>549</sub> cells when using the fluorescent dichlorofluorescein probe. Moreover, indigenous nanotalc resulted higher ROS generation than commercial nanotalc.

GSH is the most abundant nonproteinous tripeptide containing a sulfhydryl group in virtually all cells, and it plays a significant role in many biological processes. It also constitutes the first line of the cellular defense mechanism against oxidative injury and is the major intracellular redox buffer in ubiquitous cell types (Meister, 1989). GSH acts as a cosubstrate in the GSH peroxidase-catalyzed reduction of hydrogen peroxide or lipid peroxides (Forman et al., 1997) leading to its depletion. Previous studies demonstrated that ROS generation following GSH depletion caused mitochondrial damage (Martensson et al., 1989; Meister, 1995), which has been implicated in apoptosis (Green and Reed, 1998). There was a significant depletion of GSH between the control and the treated groups except for indigenous microtalc at 50 µg/ml. In terms of GSH depletion, indigenous nanotalc was found to be the most toxic.

In the toxicity mechanism of minerals, the iron content has been a key factor. Iron-dependent ROS generation from fibers results in the generation of hydroxyl radicals through the Fenton reaction and the Haber-Weiss cycle. Iron-dependent LPO could be important, since this process requires redox cycling of iron and does not necessarily require H<sub>2</sub>O<sub>2</sub> or ROS (Halliwell and Gutteridge, 1990). Indeed, iron has a key role in both the initiation and propagation of LPO, leading to the generation of peroxy and alkoxy radicals as well as lipid peroxides (Halliwell and Gutteridge, 1990). It has been known for several years that the surface iron (II) or leachable iron (II) on mineral surfaces reduces molecular oxygen to superoxide anion, which then dismutates to hydrogen peroxide. In the presence of asbestos or silica, hydrogen peroxide and superoxide react via a Fenton-like reaction driven by iron to form the potent hydroxyl radical *in vitro* leading to cellular LPO (Mossman et al., 1996). Since, LPO is a sensitive parameter for toxic effects of various environmental pollutants with oxidative properties (Krug and Culig, 1991; Beck-Speier et al., 2001; Oberdorster, 2004; Sayes et al., 2005); the authors suspected that the relatively high iron content in both the nanotalc may play a key role to yield higher ROS and in turn caused higher LPO. There are other nanomaterials, such as C<sub>60</sub>, which mediates cytotoxicity primarily through lipid peroxidation (Sayes et al., 2005; Isakovic et al., 2006) whereas carboxyfullerenes (made by certain surface modifications of C<sub>60</sub>) have been shown to impart cytoprotective activity by eliminating reactive oxygen species (ROS) and antago-



nizing the effects of the oxidative stress-dependent cytotoxicity (Dugan et al., 1997, 2001; Bogdanovic et al., 2004; Isakovic et al., 2006). Recently Scarfi et al. (2009) has reported that plasma membrane contact with quartz, a kind of silica, is sufficient to trigger membrane LPO, TNF- $\alpha$  release and cell death in mouse macrophage cell line RAW 264.7. The authors hypothesize that contact of particles with cell membranes initiate ROS generation and LPO in a ratio of amount of iron present in talc nanoparticles.

For a given mass compared with larger particles, the ratio of surface to total atoms or molecules increases exponentially with decreasing particle size. Particle size is thereby an essential determinant of the fraction of reactive groups on particle surface (Oberdorster et al., 2005; Nel et al., 2006). For example, several studies found that ultrafine particles of titania are more toxic than its larger counterparts having the same chemical composition (Donaldson et al., 1998; Gilmour et al., 1997; Oberdorster et al., 1992, 1995; Oberdorster, 1996, 2000). Similarly, surface area-dependent induction of oxidative stress and consequently, proinflammatory effects have been found to correlate in case of polystyrene particles by Brown et al. (2001) and Lin et al. (2006) have reported higher toxicity of the two sizes (15 and 46 nm) of silica nanoparticles than micro silica (5  $\mu$ m) on A<sub>549</sub> cells. Here two sizes (15 and 46 nm) of silica nanoparticles induced no significant differences in the toxicity and similar was the case in a study done by Sayes et al. (2006), where smaller nanoparticles of titania had effects comparable to larger nanoparticles of titania but showed a phase-dependent differential toxicity where anatase titania (photoactive phase), able to generate ROS more strongly, was 100 times more toxic than an equivalent sample of rutile titania. In the present study, both nanoparticles would have been resulted differential surface iron activity per given mass resulting in differential toxicity. When indigenous nanotalc induced toxicity is compared with indigenous microtalc, size-dependent factor becomes apparent because all the compositional factors are constant. But when commercial nanotalc (having larger surface area but lower iron content) induced toxicity is compared with indigenous microtalc, the results show a complex function of size and impurities. Since, micro talc size is very large (50–65  $\mu$ m), than commercial nanotalc (70–120 nm), perhaps size becomes the primary determinant of toxicity, resulting in higher toxicity of commercial nanotalc than indigenous micro talc.

Another pathway of free radical generation by asbestos, silica or particulates like these (e.g. talc particles) occurs via an oxidative burst when fibers and particles are phagocytised by AMs or other cell types, including alveolar epithelial cells and fibroblasts (Churg, 1996). Phagocytic cells can endocytose small particles, whereas bigger crystals and fibers are subject to so called “frustrated phagocytosis”. Experimental studies suggest that in *in vivo* conditions “frustrated phagocytosis” appears to have a dramatic influence on the sustained generation of ROS (Hansen and Mossman, 1987; Vallyathan et al., 1992). Repeated “frustrated phagocytosis” would be expected to attract more phagocytes, resulting in chronic enhanced generation of ROS, which in turn contribute to inflammatory activation, resulting in the secretion of IL-1 $\beta$  leading to the initiation of pulmonary fibrosis (Dostert et al., 2008; Cassel et al., 2008). Since, talc and asbestos are physically and chemically similar, found together in nature and being particulate structure like silica and asbestos, talc particles may also generate ROS through activation of NADPH oxidase by frustrated phagocytosis, leading to the initiation of so called talcosis particularly in occupationally exposed workers.

Antioxidants, such as  $\alpha$ -tocopherol, uric acid and L-ascorbic acid, typically prevent cellular damages caused by oxygen radicals by acting as ROS scavengers (Packer et al., 1979; Burton and Ingold, 1981). Ascorbic acid (or vitamin C) acts as a potent water soluble antioxidant in biological fluids (Frei et al., 1989, 1990) by scavenging physiologically relevant ROS and reactive nitrogen species

(RNS) (Halliwell, 1996). However, it should be noted that antioxidative potential of ascorbic acid has not been validated in certain conditions (Bowry et al., 1992; Poulsen et al., 1998; Levine et al., 1998). Ascorbic acid contributes significantly to cellular antioxidation as a water soluble chain-breaking radical scavenger (Asard, 2008) and to the recycling of plasma membrane  $\alpha$ -tocopherol (vitamin E) via the reduction of the  $\alpha$ -tocopheroxyl radical (Aguirre and May, 2008). The latter activity may assist ascorbic acid to protect against LPO in membranes (May et al., 1998). We, therefore, tested the LPO preventive potential of antioxidant L-ascorbic acid, on nanotalc and microtalc challenged A<sub>549</sub> cells. Results show that 1.5 mM L-ascorbic acid effectively, but not completely, inhibited MDA level induced by talc nanoparticles. Determining the optimum concentration of ascorbic acid that might completely suppress LPO without causing any side-effect is a matter of concern (Halliwell, 1999) and the evaluation of interrelationship between LPO and chelating effect of iron present on the surface of talc particles by deferoxamine mesylate on LPO is under investigation. Oxidative stress is known to elicit varying effects on the activity of antioxidant enzymes. The three primary scavenger enzymes involved in detoxifying ROS in mammalian systems are catalase, superoxide dismutase and glutathione peroxidase (Matés et al., 1999). For example the activity of GPx can provide important clue about the consumption rate of GSH in enzymatic detoxification of ROS. The activity of antioxidant enzymes can therefore provide further insight in understanding the mechanism of toxicity caused by talc particles and is currently under investigation.

## 5. Conclusion

We have presented a preliminary data on the toxicity response elicited by the two types of talc nanoparticles, depending on their different geological origin. Since, talc with a multitude of physical and functional characteristics due to different geological context and deposits, is used for particular applications, so occupational and consumer exposures to talc and its toxic effects are likely to vary accordingly, which is obvious in this study. The cytotoxicity seems to be due to primarily through induction of LPO, as a potential mechanism of toxicity discussed above. Addition of 1.5 mM of L-ascorbic acid, a ROS scavenger, significantly, though not completely, reduced LPO. Data clearly suggest that exposure of talc, particularly nanopowder, should be protected in humans at risk of occupational as well as domestic exposure.

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# Exhibit W

# Cytotoxicity and Apoptosis Induction by Nanoscale Talc Particles from Two Different Geographical Regions in Human Lung Epithelial Cells

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**ABSTRACT:** We have characterized the physicochemical properties of nanotalc particles from two different geographical regions and examined their toxicity mechanisms in human lung epithelial (A549) cells. Indigenous nanotalc (IN) of Indian origin and commercial nanotalc (CN) of American origin were used in this study. Physicochemical properties of nanotalc particles were characterized by X-ray diffraction (XRD), transmission electron microscopy (TEM), energy dispersive X-ray spectroscopy (EDS), Brunauer-Emmet-Teller (BET), and dynamic light scattering (DLS). Results showed that both IN and CN particles significantly induce cytotoxicity and alteration in cell cycle phases. Both IN and CN particles were found to induce oxidative stress indicated by induction of reactive oxygen species (ROS), lipid peroxidation, and depletion of antioxidant levels. DNA fragmentation and caspase-3 enzyme activation due to IN and CN particles exposure were also observed. We further showed that after iron chelation, IN and CN particles produce significantly less cytotoxicity, oxidative stress, and genotoxicity to A549 cells as compared with nonchelated particles. In conclusion, this study demonstrated that redox active iron plays significant role in the toxicity of IN and CN particles, which may be mediated through ROS generation and oxidative stress. © 2012 Wiley Periodicals, Inc. *Environ Toxicol* 29: 394–406, 2014.

**Keywords:** nanotalc particles; physicochemical characterization; iron chelation; toxicity; apoptosis

## INTRODUCTION

Talc is a mineral compound  $[\text{Mg}_3\text{Si}_4\text{O}_{10}(\text{OH})_2]$  with unique attributes and significant commercial importance.

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Talc is widely used due to its intrinsic properties such as high thermal stability, low electrical conductivity, good absorption and adsorption properties, and high crystallinity (Pérez-Maqueda et al., 2005; Nkoubou et al., 2008). Talc is utilized in various applications including paper, paint, cosmetic, plastic, ceramic, pesticide, and pharmaceuticals (Carretero, 2002; Bizi et al., 2003; Petit et al., 2004). Hence, occupational and consumer exposures to talc particles are wide and complex (Jaynes and Zartman, 2005). It has been reported that talc mine workers show higher rates of lung cancer and other respiratory diseases (National Toxicology Program, 1993). Epidemiologic evidence also suggests a possible association between genital use of talcum powder and risk of ovarian cancer (Wild,

2006; Buz'Zard and Lau, 2007; Gates et al., 2008; Langseth et al., 2008). Talc also appears to induce reactive oxygen species (ROS) generation, oxidative stress, and inflammation (Harlow and Hartge, 1995; Buz'Zard and Lau, 2007).

Due to enhanced intrinsic properties, nanoscale talc particles are extensively utilized in many commercial and industrial products (Akhtar et al., 2008; Balamurugan and Maiti, 2010; Sakthivel and Pitchumani, 2011). Despite the wide-spread applications, there is a serious lack of information concerning the mechanisms of toxicity of nanotalc particles. Previously, we have observed that human cells exposed to nanotalc particles induce oxidative stress-mediated cytotoxicity (Akhtar et al., 2010a). However, physicochemical characterization of nanotalc particles and their association with the toxicological response in human cells is still remains unclear.

There are numerous reports suggesting that ROS is an important mediator of the toxicity of minerals such as asbestos and silica (Aung et al., 2007; Akhtar et al., 2010b). It has been known for years that the surface iron (II) or leachable iron (II) on mineral surfaces reduces molecular oxygen to superoxide anion, which is then dismutated to hydrogen peroxide (Shukla et al., 2003). In the presence of asbestos or silica, hydrogen peroxide and superoxide react via a Fenton reaction and/or Haber-Weiss reaction driven by iron to form the potent hydroxyl radical in vitro leading to cellular oxidative damage (Persson et al., 2003).

The aim of this work was to characterize the physicochemical properties of nanotalc particles and to determine the role of iron in the toxicity mechanisms of nanotalc particles in human lung epithelial (A549) cells. We utilized two types of nanotalc particles from different geographical origins; indigenous nanotalc (IN) of Indian origin and commercial nanotalc (CN) of American origin. Cytotoxicity of IN and CN particles was examined by MTT and LDH assays. Oxidative stress response of IN and CN particles was assessed by measuring reactive oxygen species (ROS), lipid peroxidation (LPO), glutathione (GSH), superoxide dismutase (SOD), and catalase (CAT). Apoptotic response of IN and CN particles was evaluated by cell cycle analysis, DNA fragmentation, and caspase-3 enzyme activity. To explore the role of iron in the toxicity of IN and CN particles, we utilized deferoxamine mesylate (DFOM), a well-known iron chelator. The physicochemical properties of IN and CN particles were characterized by X-ray diffraction (XRD), transmission electron microscopy (TEM), energy dispersive X-ray spectroscopy (EDS), Brunauer-Emmet-Teller (BET), and dynamic light scattering (DLS). The A549 cells, derived from human lung carcinoma, have been widely utilized in toxicological studies (Zhang et al., 2010; Akhtar et al., 2010a,b; Ahamed et al., 2011a,b,c).

## MATERIALS AND METHODS

### Nanotalc Particles and Reagents

We have utilized the nanotalc particles from two different geographical regions. Indigenous nanotalc (IN) particles were collected from Rajasthan, India, as reported in our previous publication (Akhtar et al., 2010a). American origin commercial nanotalc (CN) particles (size 70–12 nm) were purchased from M.K. Impex (Mississauga, Canada).

Fetal bovine serum (FBS), penicillin-streptomycin, DMEM/F-12 medium, and HBSS were purchased from Invitrogen Co. (Carlsbad, CA). MTT [3-(4,5-dimethylthiazol-2-yl)-2,5 diphenyltetrazolium bromide], 2,7-dichlorofluorescein diacetate (DCFH-DA), deferoxamine mesylate (DFOM), glutathione (GSH), thiobarbituric acid (TBA), propidium iodide (PI), RNase A, diethylenetriaminepentaacetic acid (DETAPAC), *N*-acetyl-asp-glu-val-asp-7-amido-4-trifluoromethylcoumarin (Ac-DEVD-AFC), 7-amido-4-trifluoromethylcoumarin (AFC) standard, Bradford reagent, and bovine serum albumin (BSA) were obtained from Sigma-Aldrich (St. Louis, MO). Apoptotic DNA Ladder Kit was bought from Roche. All other chemicals used were of the highest purity available from commercial sources.

### Characterization of Nanotalc Particles

Crystalline nature of both IN and CN particles were examined by taking X-ray diffraction (XRD) pattern at room temperature with the help of PANalytical X'Pert X-ray diffractometer equipped with a Ni filtered using Cu-K $\alpha$  ( $\lambda$  = 1.54056 Å) radiations as X-ray source. Morphology and size of IN and CN particles were examined by field emission transmission electron microscopy (FETEM) (JEM-2100F, JEOL Inc., Tokyo, Japan) at an accelerating voltage of 200 kV. To check the purity of IN and CN particles, an energy dispersive X-ray spectroscopy (EDS) analysis was performed. Brunauer-Emmet-Teller (BET) surface area measurement of IN and CN particles was determined by multipoint nitrogen adsorption at 77 K using a Beckman Coulter SA3100 device.

Dynamic light scattering (DLS) and laser Doppler velocimetry (LDV) for the characterization of hydrodynamic size and zeta potential ( $\zeta$ ) of IN and CN particles in distilled water and cell culture media were performed on a Malvern Instruments Zetasizer Nano-ZS instrument as described by Murdock et al. (2008).

### Treatment of Nanotalc Particles with Deferoxamine Mesylate

We treated both IN and CN particles with DFOM for iron chelation. In brief, IN and CN particles were incubated with 10 mM DFOM at a concentration of 1000  $\mu$ g/mL for

20 h as described by Aung et al. (2007). Then particles were washed three times with cell culture medium by centrifuging at 4000 rpm for 10 min followed by resuspension.

### Cell Culture and Exposure to Nanotalc Particles

Human lung epithelial (A549) cells were obtained from National Centre for Science (NCCS), Pune, India. Cells were used between passages 10 and 20. Cells were cultured in DMEM/F-12 medium supplemented with 10% FBS and 100 U/mL penicillin-streptomycin at 5% CO<sub>2</sub> and 37°C. At 85% confluence, cells were harvested using 0.25% trypsin and were subcultured into 75 cm<sup>2</sup> flasks, 6-well plates, or 96-well plates according to selection of experiments. Cells were allowed to attach the surface for 24 h before treatment. IN and CN particles were suspended in cell culture medium and diluted to a appropriate concentration (200 µg/mL). Suspension of nanotalc particles were then sonicated using a sonicator bath at room temperature for 10 min at 40 W to avoid particles agglomeration before administration to the cells. The selection of the 200 µg/mL concentration of nanotalc particles was based on our previous publication (Akhtar et al., 2010a). All the data presented in this study was that of 48 h exposure. Cells not exposed to nanotalc particles served as controls in each experiment.

### Cell Viability Assay

Viability of A549 cells after exposure to nanotalc particles was assessed by MTT assay as described by Mossman (1983). The MTT assay assesses the mitochondrial function by measuring ability of viable cells to reduce MTT into blue formazon product. In brief, 10,000 cells per well were seeded in 96-well plate and exposed to IN and CN particles at the concentration of 200 µg/mL for 48 h. After the exposure completed, the medium was removed from each well to avoid interference of particles and replaced with new medium containing MTT solution in an amount equal to 10% of culture volume, and incubated for 3 h at 37°C until a purple colored formazan product developed. The resulting formazan product was dissolved in acidified isopropanol. Further, the 96-well plate was centrifuged at 2500 rpm for 5 min to settle down the remaining particles present in the solution. Then, a 100 µL supernatant was transferred to other fresh wells of 96-well plate and absorbance was measured at 570 by using a microplate reader (FLUOstar-Omega).

### Lactate Dehydrogenase Leakage Assay

Lactate dehydrogenase (LDH) is an enzyme widely present in cytosol that converts lactate to pyruvate. When plasma

membrane integrity is disrupted, LDH leaks into culture media and its extracellular level is elevated. LDH assay was carried out with the method described earlier (Wroblewski and LaDue, 1955; Welder et al., 1991). In brief, 10,000 cells per well were seeded in 96-well plate and exposed to IN and CN particles at the concentration of 200 µg/mL for 48 h. After the exposure completed, the 96-well plate was centrifuged at 2500 rpm for 10 min to get the cell culture media. Then, a 100 µL of culture media transferred to new fresh tube containing 100 µL of sodium pyruvate (2.5 mg/mL phosphate buffer) and 100 µL of reduced nicotinamide adenine dinucleotide (NADH) (2.5 mg/mL phosphate buffer) in a total volume of 3.0 mL (0.1 M potassium phosphate buffer, pH 7.4). The rate of NADH oxidation was determined by following the decrease in absorbance at 340 nm for 3 min at 30-s interval using a spectrophotometer (Thermo-Spectronic).

### Cell Cycle Analysis

Cell cycle distribution was assayed by determining DNA content. Cells were treated with IN and CN particles for 48 h. After exposure, cells were fixed in 3% (w/v) paraformaldehyde for 10 min, permeabilized on ice in phosphate buffer saline-0.5% Triton X-100 for 15 min, washed and resuspended in 0.5 ml of phosphate buffer saline containing 1% FBS, 1 mg/ml RNaseA, and 50 µg/ml propidium iodide. The samples were incubated for 30 min at 37°C. The data were acquired and analyzed on FACS-Calibur flow cytometer (Becton-Dickinson LSR II, San Jose, CA) using Cell Quest 3.3 software.

### Measurement of Reactive Oxygen Species

For the measurement of ROS generation, cells were cultured in 12-well plate. The production of intracellular ROS was measured using 2,7-dichlorofluorescein diacetate (DCFH-DA) (Wang and Joseph, 1999). The DCFH-DA passively enters the cell where it reacts with ROS to form the highly fluorescent compound dichlorofluorescein (DCF). Briefly, 10 mM DCFH-DA stock solution (in methanol) was diluted in culture medium without serum or other additive to yield a 100 µM working solution. After exposure to IN and CN particles, cells were washed twice with HBSS and then incubated in 1 mL working solution of DCFH-DA at 37°C for 30 min. Cells were lysed in alkaline solution and centrifuged at 3000 rpm for 10 min. Then, a 200 µL supernatant (from 12-well plate) was transferred to the fresh well of black 96-well plates and fluorescence was measured using at 485 nm excitation and 520 nm emission using a microplate reader (FLUOstar-Omega). The values of ROS were expressed as percent of fluorescence intensity relative to controls.



### Membrane Lipid Peroxidation Assay

The extent of membrane lipid peroxidation (LPO) was estimated by measuring the formation of thiobarbituric acid reactive species (TBARS) using the method of Ohkawa et al. (1979). Briefly, cells were cultured in 75 cm<sup>2</sup> culture flask and exposed to IN and CN particles at the concentration of 200 µg/mL for 48 h. After the treatment, a 200 µL of cell suspension was mixed with 800 µL of LPO assay cocktail containing TBA (0.4%, w/v), sodium dodecyl sulphate (0.5%, w/v), and acetic acid (5 %, v/v). Reaction mixture was then incubated at 95°C for 1 h. After cooling to room temperature the reaction mixture was centrifuged at 5000 rpm for 5 min. The absorbance of the supernatants was read at 532 nm against the standard. The amount of TBARS was expressed as nmol/mg protein.

### Intracellular Glutathione Assay

Intracellular GSH was quantified using the method of Hissin and Hilf (1976). Briefly, cells were cultured in 75 cm<sup>2</sup> culture flask and exposed to IN and CN particles at the concentration of 200 µg/mL for 48 h. After the exposure completed, cells were lysed in 20 mM Tris (pH 7.0) and the centrifuged at 10,000 rpm for 10 min at 4°C. Further, protein of the supernatant was precipitated using 1% perchloric acid and again centrifuged at 10,000 rpm for 5 min at 4°C to get supernatant. Then 20 µL of supernatant was mixed with 160 µL of 0.1M potassium phosphate-5 mM EDTA buffer (pH 8.3) and 20 µL O-phthalaldehyde (1 mg/mL in methanol) in a black 96-well plate. After 2 h of incubation at room temperature in the dark, fluorescence was measured at emission wavelength of 460 nm and excitation wavelength of 350 nm. The amount of GSH was expressed as nmol GSH/mg protein.

### Antioxidant Enzymes Activity Assay

Cells were cultured in 75 cm<sup>2</sup> culture flask and exposed to IN and CN particles at the concentration of 200 µg/mL for 48 h. After the exposure completed, cells were harvested in ice-cold phosphate buffer saline and washed twice with phosphate buffer saline at 4°C. The cell pellets were then lysed in cell lysis buffer. Following centrifugation (10,000 rpm for 10 min 4°C) the supernatant (i.e. cell lysate) was maintained on ice until assayed for activity of superoxide dismutase (SOD) and catalase (CAT) enzymes. The total SOD was determined using pyrogallol assay following the procedure described by Marklund and Marklund (1974), based on the competition between pyrogallol oxidation by superoxide radicals and superoxide dismutation by SOD, and spectrophotometrically read at 420 nm. The amount of SOD inhibiting the reaction rate by 50% in the given assay conditions was defined as one

unit of SOD. The results were expressed as units/min/mg protein.

CAT activities were assayed by the method described by Claiborne (1985). One unit of CAT activity is defined as the amount of enzyme that decomposes 1 µmol H<sub>2</sub>O<sub>2</sub>/min. CAT activities were given as µmol H<sub>2</sub>O<sub>2</sub> decomposed/min/mg protein.

### DNA Ladder Assay

Cells were cultured in 6-well plate and exposed to IN and CN particles at the concentration of 200 µg/mL for 48 h. At the end of exposure DNA was extracted using an apoptotic DNA Ladder Kit (Roche, Cat# 11835246001). The extracted DNA was then evaluated on a 1% agarose gel using ethidium bromide. DNA fragmentation pattern was documented by a gel documentation system.

### Assay of Caspase-3 Enzyme

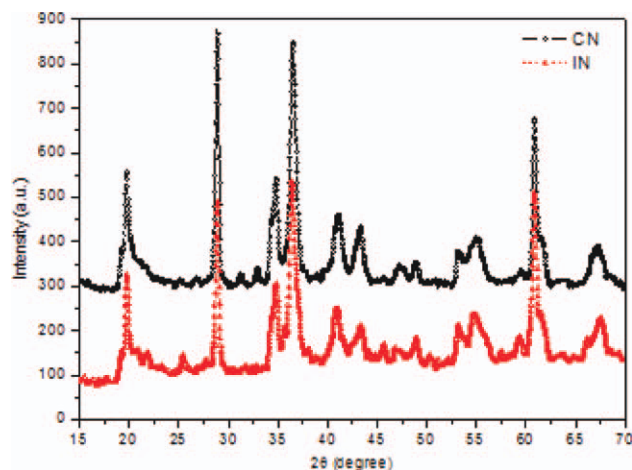
Cells were cultured in 6-well plate and exposed to IN and CN particles at the concentration of 200 µg/mL for 48 h. Activity of caspase-3 enzyme was determined using a standard fluorometric microplate assay (Walsh et al., 2008) with some modifications. A reaction mixture containing 30 µL of cell lysate, 20 µL of Ac-DEVD-AFC (caspase-3 substrate), and 150 µL of protease reaction buffer (50 mM Hepes, 1 mM EDTA, and 1 mM DTT), pH 7.2, was incubated for 15 min. Fluorescence of reaction mixture was measured at 5 min interval for 15 min at excitation/emission wavelengths of 430/535 nm using a microplate reader (FLUOstar-Omega). A standard of 7-amido-4-trifluoromethylcoumarin (AFC) ranging from 5 to 15 µM was prepared and its fluorescence was recorded for calculation of caspase-3 activity in terms of pmol AFC released/min/mg protein.

### Estimation of Protein

The protein content was measured by the method of Bradford (1976) using Bradford reagent (Sigma-Aldrich, St. Louis, MO), along with bovine serum albumin as standard.

### Statistics

All the data represented in this study are means ± SD of three identical experiments made in three replicate. Statistical significance was determined by one-way analysis of variance (ANOVA) followed by Dunnett's multiple comparison test. Significance was ascribed at  $p < 0.05$ . All analyses were conducted using the Prism software package (GraphPad Software).



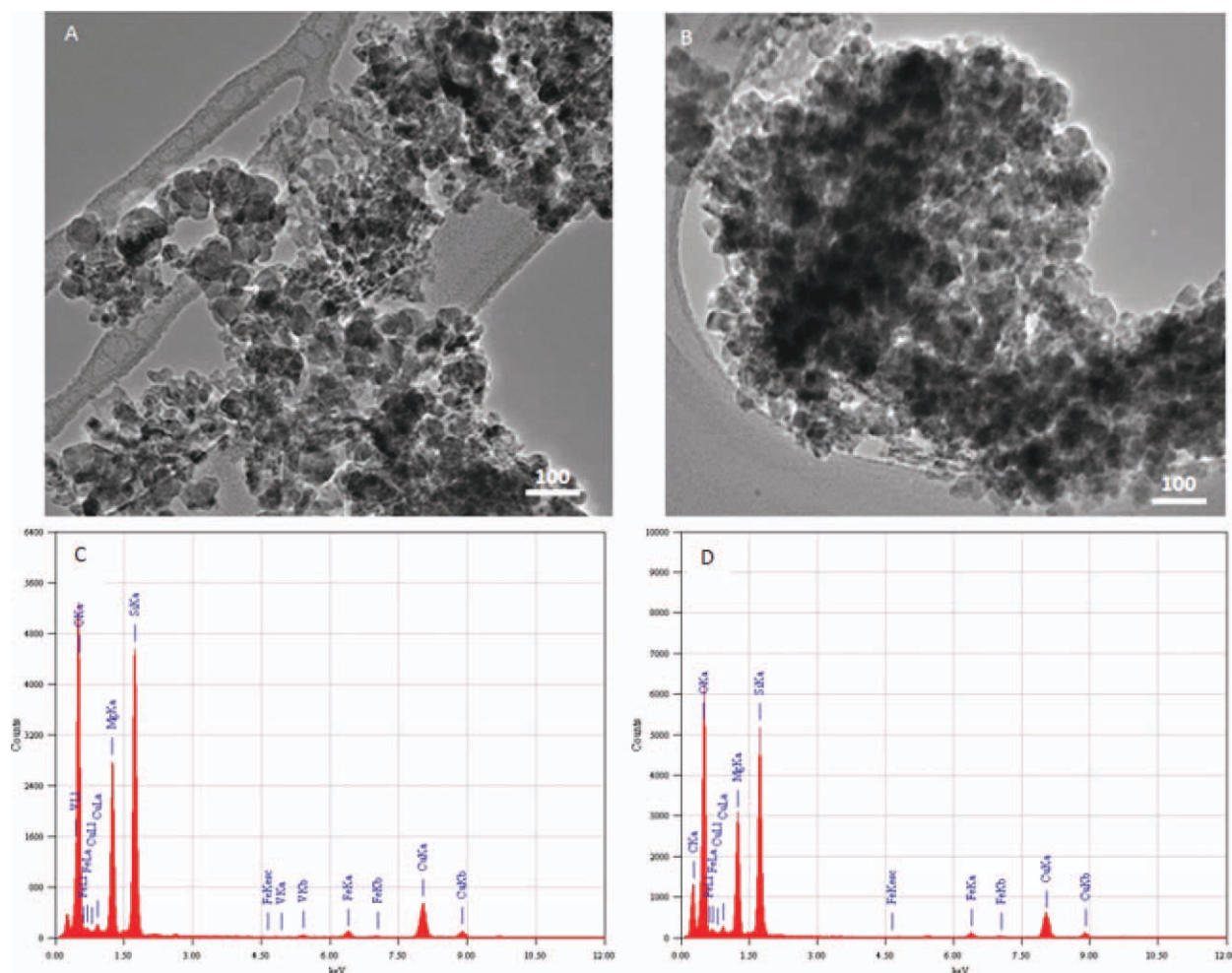
**Fig. 1.** XRD pattern of two types of nanotalc particles. IN; indigenous nanotalc particles, CN; commercial nanotalc particles. [Color figure can be viewed in the online issue, which is available at [wileyonlinelibrary.com](http://wileyonlinelibrary.com).]

## RESULTS

### Characterization of IN and CN Particles

Characterization of IN and CN particles was performed using a combination of XRD, TEM, DLS, zeta-potential, and BET in order to provide clear insight into crystalline nature, morphology, particle size, surface property, and chemical composition. These properties are necessary for a better understanding of nanotoxicology.

Figure 1 represents the XRD pattern of IN and CN particles. Image clearly exhibits that the crystalline nature of both IN and CN particles were same. The average size of nanocrystals calculated from the XRD results using Scherrer's equation (Patterson, 1939) was found to be 93 and 89 nm for IN and CN particles, respectively. Figure 2(A,B) show the typical TEM images of IN and CN particles, respectively. Images show that particles are aggregated. We never found small independent crystals in the TEM images.



**Fig. 2.** TEM characterization of nanotalc particles. (A) FETEM of indigenous nanotalc particles, (B) FETEM of commercial nanotalc particles, (C) EDS spectrum of indigenous nanotalc particles, and (D) EDS spectrum of commercial nanotalc particles. [Color figure can be viewed in the online issue, which is available at [wileyonlinelibrary.com](http://wileyonlinelibrary.com).]

**TABLE 1. Physicochemical properties of two types of nanotalc particles**

	Indigenous Nanotalc (IN)	Commercial Nanotalc (CN)
Average XRD size (nm)	93	89
Average TEM size (nm)	94	91
Surface area (m <sup>2</sup> /g)	15.4	15.7
Hydrodynamic size (nm)		
Distilled water	782	735
Cell culture medium	671	643
Zeta potential (–mV)	20.3	20.8
Iron content (%) <sup>a</sup>	0.19	0.08

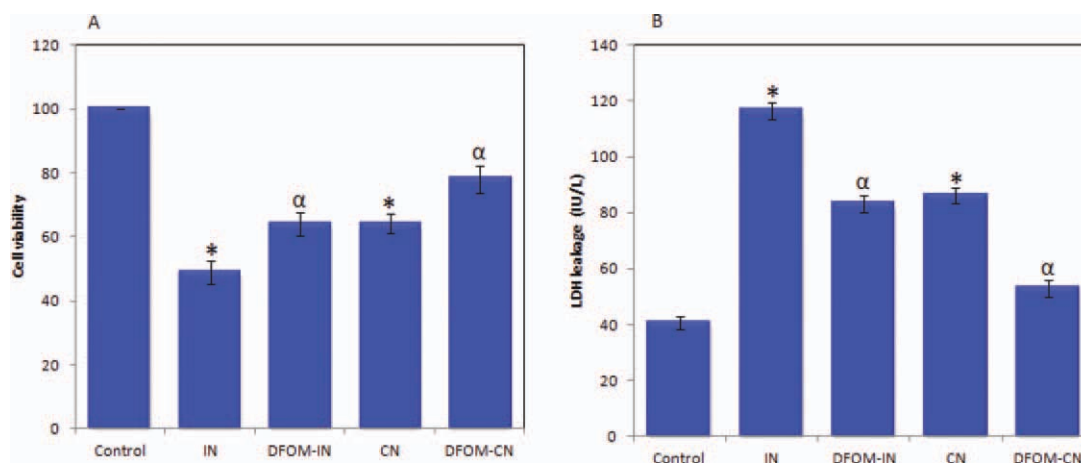
<sup>a</sup>This information is obtained from our previous publication (Akhtar et al., 2010a).

The average TEM size of IN and CN particles were 94 and 91 nm, respectively, which were consistent with the value observed by XRD. The EDS spectra of IN and CN particles are given in Figure 2(C,D), respectively. The presence of Cu and C signals was from the carbon-coated-copper TEM-grid. Presence of iron peaks in both IN and CN particles are in agreement with our previous reports where atomic absorption spectroscopy data showed that 0.19% and 0.08% of iron present in IN and CN particles, respectively (Akhtar et al., 2010 a). The specific surface area of IN and CN particles determined by BET was 15.4 and 15.7 m<sup>2</sup>/g respectively.

The physicochemical properties of IN and CN particles are listed in Table 1. All the data from XRD, electron microscopy, and associated techniques was obtained under high vacuum and constitutes the size, morphology, and composition analysis characteristics of nanotalc particles. However, once the nanotalc particles were introduced aqueous media, the sizes changed to approximately 5 to 10 times of the primary size. The average hydrodynamic size of IN and CN particles in distilled water was 782 nm and 735 nm while in cell culture media was 671 and 643 nm, respectively. The higher size of IN and CN particles in aqueous state as compared to XRD and TEM results was due to the tendency of particles to aggregate in the aqueous state. This finding is supported by other investigators (Murdock et al., 2008) and has been briefly discussed in our previous publications (Ahamed et al., 2010a,b). The tendency of particles to form aggregates depends strongly on the surface charge. The particle charge, determined as zeta-potential by laser doppler velocimetry (LDV) was –20.3mV and –20.8 for IN and CN, respectively.

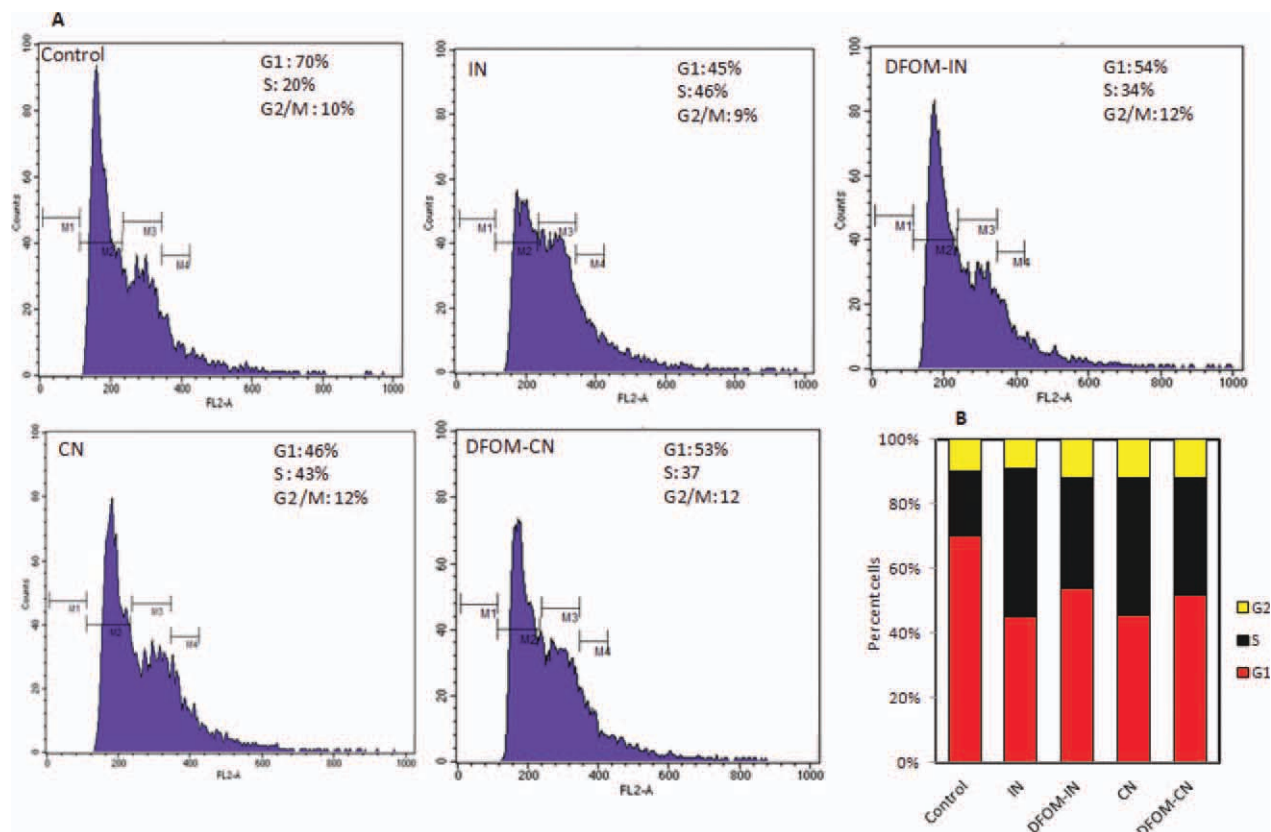
### IN and CN Particles Induced Cytotoxicity

We examined the cell viability (MTT assay) and membrane damage (LDH leakage) as cytotoxicity end points. MTT results demonstrated that both IN and CN particles induced significant reduction in cell viability. The MTT reduction



**Fig. 3.** Comparative effects of nanotalc particles and iron-chelated nanotalc particles on cell viability and LDH release in human lung epithelial A549 cells. Cells were treated with two types of nanotalc particles at the concentration of 200 μg/mL for 48 h. Iron chelator deferoxamine mesylate (DFOM) was co-exposed with nanotalc particles. At the end of treatment MTT and LDH assays were determined as described in materials and methods. (A) MTT assay and (B) LDH assay. Data represented are mean ± SD of three identical experiments made in three replicates. \*Statistically significant difference in cell viability reduction and LDH release as compared with the controls ( $p < 0.05$  for each). <sup>α</sup>Iron chelation by DFOM significantly reduces the cytotoxicity caused by nanotalc particles ( $p < 0.05$  for each). IN; indigenous nanotalc particles, CN; commercial nanotalc particles, DFOM-IN; indigenous nanotalc particles treated with DFOM, DFOM-CN; commercial nanotalc particles treated with DFOM. [Color figure can be viewed in the online issue, which is available at [wileyonlinelibrary.com](http://wileyonlinelibrary.com).]





**Fig. 4.** Comparative effects of nanotalc particles and iron-chelated nanotalc particles on cell cycle in human lung epithelial A549 cells. Cells were treated with two types of nanotalc particles at the concentration of 200  $\mu\text{g/mL}$  for 48 h. Iron chelator deferoxamine mesylate (DFOM) was coexposed with nanotalc particles. At the end of treatment cell cycle was analyzed as described in materials and methods. (A) Raw data generated by flow cytometric analysis of selected representative samples. The y-axis denotes cell count and the x-axis represents DNA content. M1, M2, M3, and M4 represent the SubG1, G1, S, and G2/M phase, respectively. (B) Percent of the distribution of cells in the G1, S, and G2/M phase of cell cycle. IN; indigenous nanotalc particles, CN; commercial nanotalc particles, DFOM-IN; indigenous nanotalc particles treated with DFOM, DFOM-CN; commercial nanotalc particles treated with DFOM. [Color figure can be viewed in the online issue, which is available at [wileyonlinelibrary.com](http://wileyonlinelibrary.com).]

observed after 48 h at the concentration of 200  $\mu\text{g/mL}$  was 49% and 64% for IN and CN particles, respectively [Fig. 3(A)]. Both IN and CN particles were also found to induce LDH leakage in A549 cells [Fig. 3(B)]. To determine whether our observed cytotoxicity was due iron content, we treated both IN and CN particles with an iron chelator DFOM and tested the cytotoxic effect of chelated nanotalc particles in A549 cells. Results showed that iron chelated IN and CN particles induce less cytotoxicity than those of non-chelated one (Fig. 3).

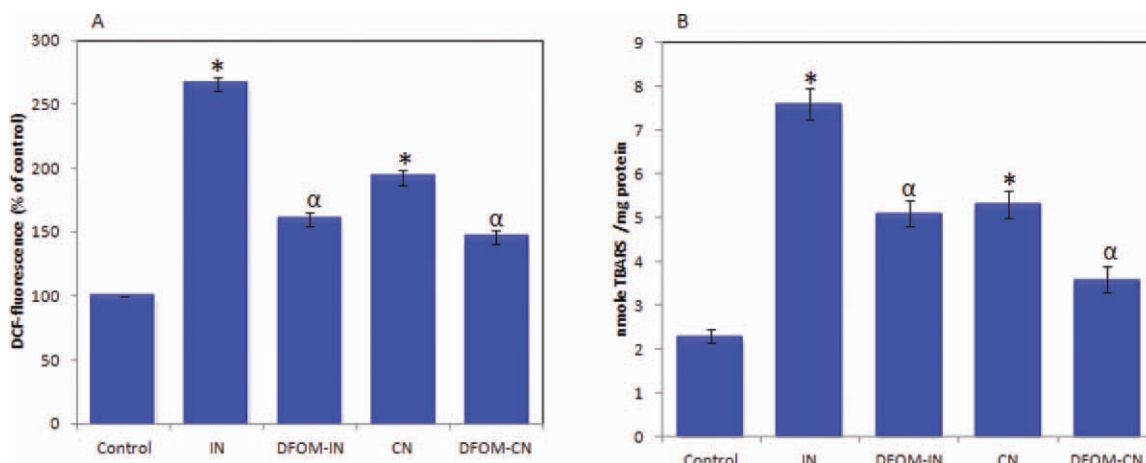
### IN and CN Particles Induced Cell Cycle Changes

Alteration in the cell cycle phases by IN and CN particles in A549 cells are shown in Figure 4. Both IN and CN par-

ticles induced significant S phase arrest. The S phase was 20% in the control. It was changed to 46% and 43% in the cells treated with IN and CN particles respectively. However, iron chelated IN and CN particles exert less effect on cell cycle arrest than those of nonchelated IN and CN particles.

### IN and CN Particles Induced Oxidative Stress

ROS generation leads to oxidative damage, which has been reported to be one of the important mechanisms of nanoparticles toxicity (Ahamed et al., 2010c; Ahamed et al., 2011a,b). The potential of IN and CN particles to induce oxidative stress was examined by measuring the ROS, LPO, GSH, SOD, and CAT in A549 cells. Results showed that both IN and CN particles induced the



**Fig. 5.** Comparative effects of nanotalc particles and iron-chelated nanotalc particles on oxidant generations in human lung epithelial A549 cells. Cells were treated with two types of nanotalc particles at the concentration of 200  $\mu\text{g/mL}$  for 48 h. Iron chelator deferoxamine mesylate (DFOM) was coexposed with nanotalc particles. At the end of treatment ROS and LPO levels were determined as described in materials and methods. (A) ROS and (B) LPO. Data represented are mean  $\pm$  SD of three identical experiments made in three replicates. \*Statistically significant difference in ROS and LPO induction as compared with the controls ( $p < 0.05$  for each).  $\alpha$ Iron chelation by DFOM significantly reduces the ROS and LPO induction caused by nanotalc particles ( $p < 0.05$  for each). IN; indigenous nanotalc particles, CN; commercial nanotalc particles, DFOM-IN; indigenous nanotalc particles treated with DFOM, DFOM-CN; commercial nanotalc particles treated with DFOM. [Color figure can be viewed in the online issue, which is available at [wileyonlinelibrary.com](http://wileyonlinelibrary.com).]

intracellular ROS and LPO levels [Fig. 5(A,B)]. Nanotalc particles induced oxidative stress was further evidenced by depletion of GSH, SOD, and CAT [Fig. 6(A,B,C)]. Moreover, chelation of iron from IN and CN particles significantly reduced the oxidative stress due to these particles.

### IN and CN Particles Induced Apoptosis

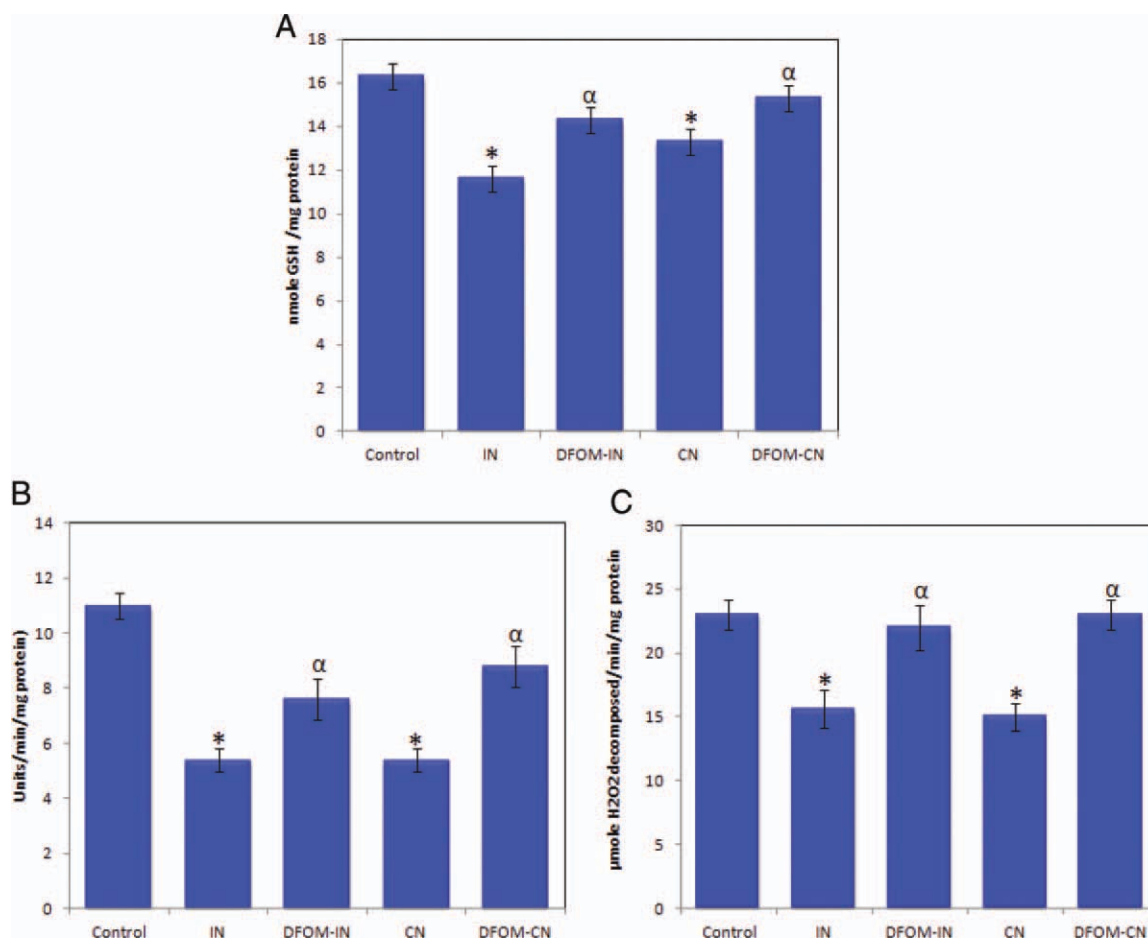
Apoptosis is executed by series of cysteine proteases known as caspases (Takadera and Ohyashiki, 2007; Tang et al., 2010). Caspase-9 activation is dependent on the release of cytochrome c from mitochondria to form the apoptosome which in turn activates caspase-3. In the present study, significant higher activity of caspase-3 enzyme was observed suggesting the involvement of caspase cascade in IN and CN particles induced apoptosis in A549 cells [Fig. 7(B)]. Figure 7(B) shows that in untreated cells, the DNA was intact whereas the cells treated with IN and CN particles had started apoptotic DNA fragmentation. Besides, iron chelation from IN and CN particles induced less DNA fragmentation as compared with the nonchelated particles.

Taken together, our data highlight the role of iron contaminant present in IN and CN particles in causing the cytotoxicity, oxidative stress, and apoptosis in human lung epithelial cells.

### DISCUSSION

Characterization of physicochemical properties of nanoparticles has been suggested in the nanotoxicology research (Murdock et al., 2008; Li et al., 2011). Several parameters including shape, size, crystal structure, purity, hydrodynamic size, aggregation of particles, and aqueous stability have already been suggested (Nel et al., 2006; Yu et al., 2009). In this study, we employed XRD, TEM, EDS, BET, and DLS techniques to characterize the physicochemical properties of IN and CN particles. XRD and TEM results indicated that both IN and CN particles were crystalline, highly aggregated, and having the iron content as a contaminant. Aggregation and stability of nanoparticles in aqueous state are major concerns in nanotoxicity research. Both IN and CN particles were also aggregated in water and cell culture media as well. Zeta potential data also showed that the aqueous suspension of both IN and CN particles were not much stable in aqueous state. The hydrodynamic size of nanotalc particles was found to be approximately seven to eight times higher than those calculated from TEM and XRD. The higher size of nanoparticles in aqueous suspension as compared with XRD and TEM sizes might be due to the tendency of particles to aggregate in aqueous state. This finding is supported by other investigators (Bai et al., 2009) and has been briefly discussed in our previous publication (Ahamed et al., 2010b).



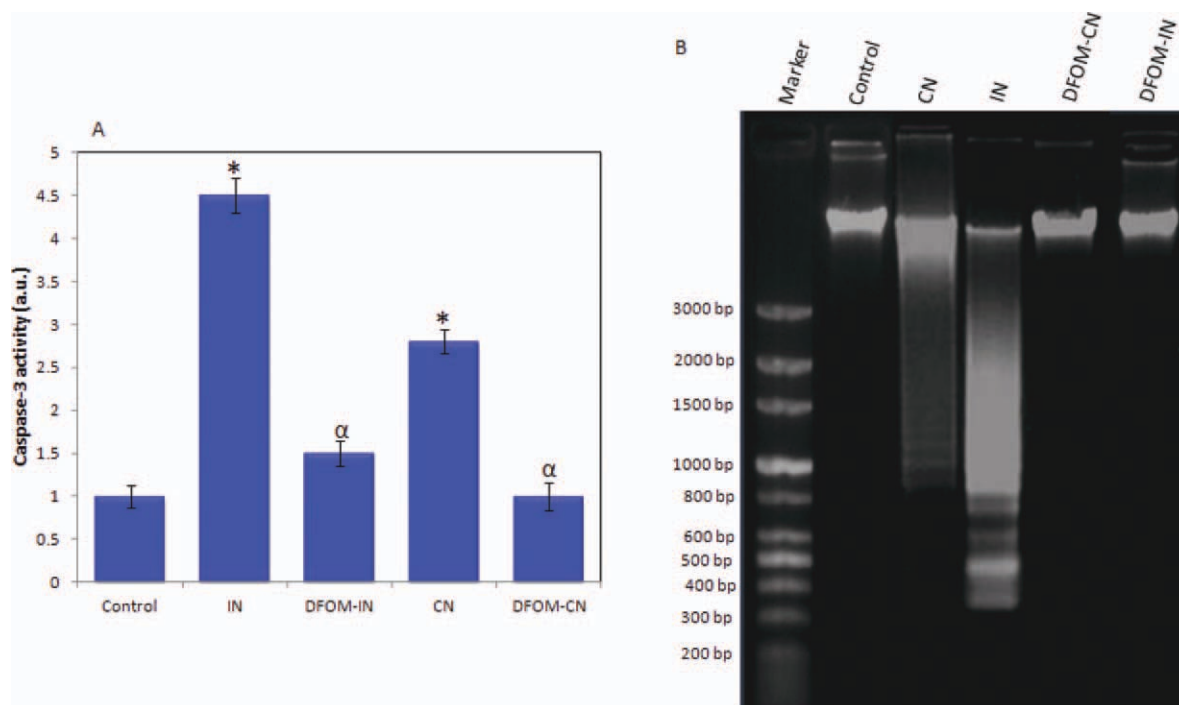


**Fig. 6.** Comparative effects of nanotalc particles and iron-chelated nanotalc particles on antioxidants reduction in human lung epithelial A549 cells. Cells were treated with two types of nanotalc particles at the concentration of 200  $\mu\text{g/mL}$  for 48 h. Iron chelator deferrioxamine mesylate (DFOM) was coexposed with nanotalc particles. At the end of treatment GSH, SOD, and CAT levels were determined as described in materials and methods. (A) GSH, (B) SOD, and (C) CAT. Data represented are mean  $\pm$  SD of three identical experiments made in three replicates. \*Statistically significant difference in GSH, SOD, and CAT reduction as compared to the controls ( $p < 0.05$  for each). <sup>α</sup>Iron chelation by DFOM significantly induces the GSH, SOD, and CAT depletion caused by nanotalc particles ( $p < 0.05$  for each). IN; indigenous nanotalc particles, CN; commercial nanotalc particles, DFOM-IN; indigenous nanotalc particles treated with DFOM, DFOM-CN; commercial nanotalc particles treated with DFOM. [Color figure can be viewed in the online issue, which is available at [wileyonlinelibrary.com](http://wileyonlinelibrary.com).]

In this study, we observed that IN and CN particles induced cell viability reduction and membrane damage in A549 cells. Both IN and CN particles also induced the cell cycle arrest in the S phase leading to apoptosis. In a previous study, S phase arrest was observed in mouse peritoneal macrophages (RAW264.7) exposed to silver nanoparticles (Park et al., 2010), and S phase arrest was also observed in human lung epithelial cells exposed to carbon black particles coated with benzo(a)pyrene (Mroz et al., 2007). Asharani et al. (2009) reported that starch-coated silver NPs induced G2/M phase arrest and DNA damage in human glioblastoma cells and fibroblasts. A perturbation of

the cell cycle preceded by a reduction in cell viability associated with accumulation of cells in S phase leading to cell death is typical of compounds inhibiting DNA synthesis (Binkova et al., 2000; Park et al., 2010).

Cellular integrity is affected by oxidative stress when the production of ROS overwhelms antioxidant defense mechanism (Halliwell and Gutteridge, 1990). Our results showed that both IN and CN particles induce oxidant levels and deplete the antioxidant levels in human lung epithelial (A549) cells. LPO and ROS were significantly higher while the antioxidant GSH was significantly lower in cells treated with IN and CN particles. Antioxidant enzymes SOD and



**Fig. 7.** Comparative effects of nanotalc particles and iron-chelated nanotalc particles on apoptotic markers in human lung epithelial A549 cells. Cells were treated with two types of nanotalc particles at the concentration of 200  $\mu\text{g/mL}$  for 48 h. Iron chelator deferoxamine mesylate (DFOM) was coexposed with nanotalc particles. At the end of treatment DNA ladder and caspase-3 activity were determined as described in materials and methods. (A) Caspase-3 activity. Data represented are mean  $\pm$  SD of three identical experiments made in three replicates. \*Statistically significant difference in caspase-3 activation as compared with the controls ( $p < 0.05$  for each).  $\alpha$ Iron chelation by DFOM significantly reduces the activity of caspase-3 by nanotalc particles ( $p < 0.05$  for each). (B) Representative image of DNA fragmentation. IN; indigenous nanotalc particles, CN; commercial nanotalc particles, DFOM-IN; indigenous nanotalc particles treated with DFOM, DFOM-CN; commercial nanotalc particles treated with DFOM. [Color figure can be viewed in the online issue, which is available at [wileyonlinelibrary.com](http://wileyonlinelibrary.com).]

CAT levels were also significantly lower in exposed cells. GSH constitutes the first line of the cellular defense mechanism against oxidative injury and is the major intracellular redox buffer in ubiquitous cell types (Meister, 1989). GSH acts as a cosubstrate in the GSH peroxidase-catalyzed reduction of hydrogen peroxide or lipid peroxides (Forman et al., 1997) leading to its depletion. Previous studies demonstrated that ROS generation following GSH depletion caused mitochondrial damage (Martensson et al., 1989), which has been implicated in apoptosis (Green and Reed, 1998). Enzymes such as SOD and CAT are meant for nullifying cellular oxidative stress. SOD catalyzes the dismutation of superoxide anion ( $\text{O}_2^-$ ) to hydrogen peroxide ( $\text{H}_2\text{O}_2$ ). CAT reduces hydrogen peroxide ( $\text{H}_2\text{O}_2$ ) to water ( $\text{H}_2\text{O}$ ) and oxygen ( $\text{O}_2$ ) (Claiborne, 1985).

The activity of caspase-3 enzyme was significantly higher in cells treated with IN and CN particles. Apoptotic DNA fragmentation was observed in cells exposed to IN

and CN particles. Caspases are activated in response to diverse cell death stimuli and ultimately dismantle the cell through restricted proteolysis of numerous cellular proteins that (Timmer and Salvesen, 2007). The activated caspase-3 is capable of autocatalysis as well as cleaving and activating other members of the caspase family, leading to rapid and irreversible apoptosis (Wang et al., 1996). Our previous studies also reported that different types of nanoparticles have potential to induce apoptosis in different kind of cells (Ahamed et al., 2010a; 2010b; 2010c; Ahamed et al., 2010b,c; 2011a).

In the toxicity mechanism of minerals, the iron content has been a key factor. In the present study, EDS analysis showed the presence of iron contamination in both IN and CN particles. These results are in agreement with our previous report where atomic absorption spectroscopy showed the presence of 0.19% and 0.08% of iron in IN and CN particles respectively (Akhtar et al., 2010a). Iron-dependent

ROS generation from fibers results in the generation of hydroxyl radicals through the Fenton reaction and the Haber-Weiss cycle. Iron-dependent ROS generation requires redox cycling of iron and does not necessarily require  $H_2O_2$  or ROS (Halliwell and Gutteridge, 1990). The differential amount of iron present in the two types of nanotalc particles prompted us to investigate the role of iron by sequestering them with an iron chelator, deferoxamine mesylate (DFOM). Sequestering of redox active iron from IN and CN particles by DFOM caused significantly less cytotoxicity, oxidative stress, and genotoxicity than those of the nonchelated IN and CN particles. Similarly, incubation of crocidolite or chrysotile fibers overnight with deferoxamine (5 mM) to inactivate iron catalyzed oxygen radical production also significantly decreased asbestos-induced apoptosis (Broaddus et al., 1996). The role of iron in minerals such as asbestos or silica has been well reported in inflammation and carcinogenesis (Ghio et al., 1992; Hardy and Aust, 1995). Zastawny et al. (1995) have reported on DNA base modifications and membrane damage in cultured mammalian cells treated with iron itself. Similarly, intracellular iron was found to play a critical role in hydrogen peroxide-induced DNA damage (Barboudi et al., 2001). It is also worth to mention that IN particles caused higher toxicity to A549 cells than those of CN particles. This might be due to higher amount of iron present in IN particles (0.19%) as compared with the CN particles (0.08%).

In conclusion, both IN and CN particles significantly induced cytotoxicity, oxidative stress, and apoptosis in human lung epithelial cells. Further, chelation of iron from IN and CN particles by deferoxamine mesylate treatment caused significantly less toxicity as compared to non-chelated IN and CN particles. Therefore, iron content plays a significant role in the toxicity of IN and CN particles, which may be mediated through ROS generation and oxidative stress. This study suggests that one must be very careful regarding the metal impurities like iron present in nanotalc particles before commercial and industrial applications.

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# Exhibit Y

**IN THE UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF NEW JERSEY**

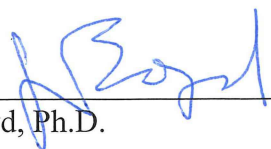
**IN RE: JOHNSON & JOHNSON TALCUM  
POWDER PRODUCTS MARKETING, SALES  
PRACTICES AND PRODUCTS LIABILITY  
LITIGATION**

**MDL NO. 16-2738 (FLW) (LHG)**

***THIS DOCUMENT RELATES TO ALL CASES***

**EXPERT REPORT OF JEFF BOYD, PHD  
FOR GENERAL CAUSATION *DAUBERT* HEARING**

Date: February 25, 2019

  
\_\_\_\_\_  
Jeff Boyd, Ph.D.

## **I. BACKGROUND AND QUALIFICATIONS**

I am professor (with tenure) and chair of the Department of Human and Molecular Genetics and professor of Obstetrics and Gynecology, as well as associate dean for Basic Research and Graduate Programs at the Herbert Wertheim College of Medicine at Florida International University. I also serve as associate deputy director, Translational Research and Genomic Medicine, at the Miami Cancer Institute of Baptist Health South Florida. I am founding director of the Center for Genomic Medicine at the Miami Cancer Institute.

I received my bachelor's degree at Duke University and my master's and Ph.D. degrees in toxicology and biochemistry at North Carolina State University, and completed my postdoctoral training in environmental pathology at the Lineberger Comprehensive Cancer Center of the University of North Carolina at Chapel Hill. Following that, I served on the faculty (as a section head of Gynecologic Pathobiology) of the National Institute of Environmental Health Sciences, National Institutes of Health. I then joined the University of Pennsylvania as an associate professor, Division of Gynecologic Oncology, within the Department of Obstetrics and Gynecology, with a joint appointment in the Department of Genetics. From 1997-2006, I worked at Memorial Sloan-Kettering Cancer Center in New York City, where I was director of the Gynecology and Breast Research Laboratory in the Department of Surgery, and director of the Diagnostic Molecular Genetics Laboratory in the Department of Medicine. While there, I was promoted to full member (professor) with tenure-of-title. I left Sloan-Kettering to become vice president of Oncology and Research and director of the Anderson Cancer Institute at the Memorial University Medical Center in Savannah, GA. I also held appointments as professor in the Departments of Obstetrics and Gynecology, Surgery, Medicine, and Division of Basic Medical Sciences, as well as assistant dean for Research at the Mercer University School of Medicine - Savannah. From 2008-2015, immediately prior to taking my positions in Miami, I was a tenured professor and held the Robert C. Young, MD, Chair in Cancer Research at Fox Chase Cancer Center in Philadelphia, where I also served as Senior Vice President, Chief Scientific Officer, and Chief of the Division of Molecular Pathology. In addition, I was founding director of the Cancer Genome Institute.

My research focuses on the genetics and molecular genetics of gynecologic and breast cancers. I have been supported by more than \$25 million in grants from the National Institutes of Health or peer-reviewed NIH-equivalent grants, and have served as principal investigator for a National Cancer Institute Specialized Program of Research Excellence grant in ovarian cancer. Additional awards include Distinguished Cancer Scholar from the Georgia Cancer Coalition (2006) and the Rosalind Franklin Award for Excellence in Ovarian Cancer Research from the Ovarian Cancer National Alliance (2015). I have authored or co-authored more than 200 articles, reviews, book chapters and editorials on the molecular and genetic bases of gynecologic or breast cancers, and been invited to present more than 150 lectures on these topics throughout the world. I have served as a peer reviewer in many capacities, including as a standing member of scientific review groups of the National Institutes of Health, the Department of Defense cancer research program, and the American Cancer Society, and as an editorial board member for seven scientific and clinical journals. I have also served as an ad hoc peer reviewer for approximately 45 scientific and clinical journals. Among my many committee and board

memberships, I served as chair of the Scientific Advisory Committee for the Ovarian Cancer Research Fund (Alliance) for nine years, and am currently a member of the Board of Directors for the Society of Gynecologic Oncology. My current research interests include the histogenesis (cell of origin) of ovarian carcinoma, the comprehensive genomic characterization of ovarian cancer stem cells, and the genomic basis of diethylstilbestrol (DES)-induced carcinogenesis of the cervix and vagina of women exposed to DES in utero.

## **II. SCOPE OF REPORT**

I was asked to opine on Dr. Ghassan Saed's expert report based on my experience as a molecular biologist and cancer researcher, and in particular, whether this research supports the biological plausibility of plaintiffs' theory that perineal talc use causes ovarian cancer. All of the opinions in this report are stated to a reasonable degree of scientific certainty. I am being compensated at the rate of \$600 per hour for my work on this matter and \$1200 per hour for deposition and other testimony.

## **III. BACKGROUND ON OVARIAN CANCER**

Ovarian cancer is a term that embraces several closely-related malignancies. Of most relevance here is epithelial ovarian carcinoma (EOC), which comprises several histological subtypes that together account for approximately 90% of all cases of "ovarian cancer." These subtypes include serous, endometrioid, clear cell and mucinous EOCs. Although the histogenesis (cell of origin) of these cancers remains relatively poorly understood, it has been established that the pathogenesis of the distinct subtypes is not entirely overlapping. For example, a proportion of serous EOCs are now believed to arise in the fallopian tube, while some proportion of clear cell and endometrioid EOCs are believed to arise from implants of endometriosis on the ovary. It should also be noted that from a clinical perspective, carcinomas of the ovary, fallopian tube and primary peritoneal lining are generally treated identically (when matched for stage), in both surgical and medical contexts, and demonstrate a very similar clinical course. Hereafter in this report, the term "ovarian cancer" will be used as defined above.

Among the few accepted significant risk factors for ovarian cancer are rare inherited genetic mutations that affect certain genes, including *BRCA1* and *BRCA2*, which are estimated to substantially increase the lifetime risk of developing ovarian cancer to as high as 40% or 20%, respectively.<sup>1</sup> Additionally, through genome-wide associational studies (GWAS), certain other common genetic variants have been correlated with an increased risk of ovarian cancer, although these variants are associated with a substantially smaller lifetime relative risk of ovarian cancer.<sup>2</sup> Overall, genetic predisposition is currently believed to be associated with approximately 20% of

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<sup>1</sup> Kuchenbaecker KB et al., *Risks of Breast, Ovarian, and Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers*. JAMA (2017) 317(23):2402-16.

<sup>2</sup> Pharoah PD et al., *GWAS meta-analysis and replication identifies three new susceptibility loci for ovarian cancer*. Nat Genet. (2013) 45(4):362-70.

all ovarian cancers.<sup>3</sup> It is very important to recognize that ovarian cancers associated with genetic predisposition as well as those (approximately 80%) that occur “sporadically” are all associated with the acquisition and accumulation of mutations affecting multiple cancer-related genes. So-called “hereditary cancers” differ only in the sense that the first rate-limiting genetic mutation is inherited, rather than acquired. In this sense, all ovarian cancers (and indeed all cancers generally) represent a genetic disease. Multiple mutations affecting multiple genes are required for a normal cell to progress to a malignant tumor cell, regardless of the tissue of origin. The causes of these “somatic” genetic mutations acquired in the organ in which a cancer ultimately develops remain largely unknown for ovarian cancer and most other cancers. Exceptions include a strong association between chronic inhalation of tobacco smoke and lung cancer, and prolonged exposure to ultraviolet-irradiation (sunlight) and skin cancer. Even for these examples, however, it is important to note that never-smokers develop lung cancer and that individuals with very low lifetime exposures to sunlight develop melanoma. Possible mutagenic mechanisms in ovarian and other cancer types include unknown environmental exposures and pure chance. Indeed, one prominent cancer molecular geneticist recently posited that most cancer cases may simply be attributable to bad luck – genetic mutations resulting from chance errors in the ordinary replication of the cellular genome (3.3 billion base pairs per cell) whenever one cell divides into two.<sup>4</sup> If such mutations occur in certain critical genes that affect elements of the cancer cell phenotype, then tumorigenesis may ensue.

The limitations on our understanding of the causes and prevention of ovarian cancer persist notwithstanding decades of intense research efforts in this field. Underscoring these difficulties, a randomized controlled clinical trial involving more than 200,000 apparently well women attempted to assess the viability of ovarian cancer screening over the course of more than a decade. The trial was recently concluded, but shed little light on potential paths forward in identifying ovarian cancer in its earliest and potentially curable stages. As the authors summarized in the published results of this clinical trial, “[f]indings from this trial suggest that for 641 women screened annually using the multimodal strategy for 14 years, one ovarian cancer death is prevented.”<sup>5</sup> This disappointing result characterizes the challenges that remain in the area of ovarian cancer research, especially in the areas of etiology and prevention.

#### **IV. PLAINTIFFS’ EXPERTS HAVE NOT SHOWN THAT THEIR PROPOSED MECHANISMS FOR OVARIAN CARCINOGENESIS ARE PLAUSIBLE**

Plaintiffs’ experts propose that talc causes inflammation, which leads to cancer, or that inflammation causes oxidative stress, which damages DNA, which results in cancer. These

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<sup>3</sup> Walsh T et al., *Mutations in 12 genes for inherited ovarian, fallopian tube, and peritoneal carcinoma identified by massively parallel sequencing*. Proc Natl Acad Sci USA (2011) 108(44):18032-7; Norquist BM et al., *Inherited mutations in women with ovarian carcinoma*. JAMA Oncol. (2016) 2(4):482-90.

<sup>4</sup> Tomasetti C & Vogelstein B, *Variation in cancer risk among tissues can be explained by the number of stem cell divisions*. Science (2015) 347:78-81.

<sup>5</sup> Jacobs I et al., *Ovarian cancer screening and mortality in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomized controlled trial*. Lancet (2016) 387:945-56.



explanations are simplistic, speculative and lack sufficient scientific support to be deemed plausible. All suffer from the same flaw to various degrees: they depend on large leaps of faith connecting one process to another. My focus, however, is on Dr. Saed's report and the underlying study he conducted, which purportedly found that talc causes an oxidative stress response that is associated with an increased ovarian cancer risk.

As set forth below, Dr. Saed's report layers speculation upon speculation. The gap between his research (which is itself filled with many methodological flaws, described below) and elucidating the origins of ovarian cancer is very large. At most, if his research had been conducted in a reliable manner, it would show that placing relatively large amounts of talc on cell lines *in vitro* can alter the expression of certain genes, change the rates of cell proliferation and apoptosis, and increase the secretion of CA-125. But these observations have no bearing on whether ordinary use of talc in a woman's underwear (or perineal area) can cause ovarian cancer, which remains a speculative theory for which plaintiffs have offered no rational scientific support.

#### A. Study Design Issues

**Use of DMSO as Solvent:** Dr. Saed determined that he needed to apply talc through a liquid medium to the cells he wished to treat. But talc is poorly soluble in water, so he apparently chose DMSO (dimethyl sulfoxide), a "universal" solvent, in which to dissolve the talc. Dr. Saed apparently believed that he was controlling for the effects of DMSO by treating a control group of cells with the same solvent (but without talc dissolved in it).<sup>6</sup> But he apparently paid no heed to recent research that has called into question whether the use of DMSO as a solvent can alter the effect of the treatment and skew the results.<sup>7</sup> In other words, while a DMSO-only control can theoretically control for the effects of DMSO by itself, it cannot control for the possibility of an interaction between DMSO and talc or DMSO and the cells that could, in and of itself, alter the effect that talc would otherwise have on the cells (if any). Dr. Saed's failure to evaluate this possibility renders most of his results (those involving exposure of cells to talc) unreliable.

**Determination of Talc Dosage:** Dr. Saed used a very highly concentrated talc solution – 500 mg of talc per 10 ml of DMSO.<sup>8</sup> He then applied relatively enormous doses of talc – from 5 to 100 µg/ml – directly to the treated cells.<sup>9</sup> This represents a far greater talc exposure than human ovarian cells would ever be subjected to under normal physiologic conditions – including as a result of regular perineal use of talcum powder. Indeed, the evidence that *any* talc can reach the ovaries from external perineal use is weak.<sup>10</sup> Dr. Saed never estimated the amount of talc he

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<sup>6</sup> Saed Dep. Vol. I 117:4-119:10.

<sup>7</sup> See Hall MD et al., *Say no to DMSO: Dimethyl sulfoxide inactivates cisplatin, carboplatin and other platinum complexes*. Cancer Res. (2014) 74(14):3913-22.

<sup>8</sup> Saed Rep. at 14.

<sup>9</sup> *Id.*

<sup>10</sup> International Agency for Research on Cancer, *Monographs on the Evaluation of Carcinogenic Risks to Humans* Vol. 93: Carbon Black, Titanium Dioxide, and Talc 411 (2010) ("[T]he evidence for retrograde transportation of talc to the ovaries of normal women is weak" and animal studies "showed no evidence of retrograde transport (cont'd)

believes would reach the ovary or the fallopian tubes as a result of perineal dusting, despite being directly asked,<sup>11</sup> and other aspects of his deposition testimony support the conclusion that such an anatomical journey would prove improbable for talc particles. In attempting to explain why talc would not produce inflammation and cancer in the intervening areas of the female reproductive anatomy, for example, Dr. Saed repeatedly referred to the “wash” of bodily fluids that would expel particulate matter.<sup>12</sup> Dr. Saed contrasted this protective mechanism to that of the ovaries, which he claims have no mechanism for removing foreign particles.<sup>13</sup> But the logical conclusion of this argument would be that the same mechanisms of expulsion of talc from areas of the female reproductive tract distal to the ovaries (vagina, cervix, uterus, fallopian tubes) should also prevent talc from otherwise migrating – like a salmon upstream – through this wash of bodily fluids, eventually reaching the ovaries.

Even accepting that talc could reach the ovaries to some extent, however, I am aware of no research suggesting that an amount approaching the quantities involved in Dr. Saed’s study would ever reach the fallopian tubes or ovaries, and Dr. Saed appears to admit as much.<sup>14</sup> As such, Dr. Saed failed to show that the dose range he used in his studies is applicable to human exposure levels and any subsequent physiological sequela.

Moreover, Dr. Saed’s report does not articulate any reason for selecting such high doses, much less any reason why he believes a study using these mega-doses is likely to produce data relevant to carcinogenesis in humans. At his deposition, Dr. Saed suggested that he initially treated cells with an even larger dose of 1000 µg/ml, but found that this dose simply killed the cells, precluding the ability to measure any biological response, and that he, therefore, selected the lower, but still very high, doses reported in his report and manuscript.<sup>15</sup> This is an inappropriate methodology for selecting an appropriate dose range for experiments designed to test the effect of a xenobiotic (foreign chemical or substance, naturally-occurring or otherwise) on cultured human cells *in vitro*, especially when the goal is to provide evidence that such an exposure is directly linked to carcinogenesis in humans.

A fundamental tenet of toxicology is that any chemical or substance, including those generally considered completely safe or inert (for example, food or beverage ingredients, or substances that humans consume or otherwise contact routinely), will almost certainly elicit a measurable biological or physiological response from cells or organisms that are exposed *in vitro* or *in vivo*,

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of talc to the ovaries”). See Henderson WJ et al., *Talc and carcinoma of the ovary and cervix*. J Obstet Gynaecol Br Commonw. (1971) 78(3):266-72 (finding no relationship between perineal talc use and ovarian talc burden); Heller DS et al., *The relationship between perineal cosmetic talc usage and ovarian talc particle burden*. Am J Obstet Gynecol. (1996) 174(5):1507-10 (same).

<sup>11</sup> Saed Dep. Vol. I 233:8-234:5.

<sup>12</sup> *Id.* 166:1-2.

<sup>13</sup> *Id.* 165:11-166:2.

<sup>14</sup> See *id.* 233:11-234:1.

<sup>15</sup> *Id.* 55:3-12.

respectively, to any such xenobiotic when administered at an extremely high, i.e., non-physiologic, dose. That said, such biologic responses, e.g., changes in gene expression or cell proliferation, may not necessarily be associated with a “toxic” outcome, e.g., cell death or neoplastic transformation. If one is testing the hypothesis that exposure to a specific xenobiotic is plausibly linked to carcinogenesis in humans, especially if the model system is human cells cultured *in vitro*, it is only logical that the appropriate experimental design would employ a dose range compatible with an equivalent physiologic exposure *in vivo*, if the intent is to argue that the biological responses seen *in vitro* are somehow related to the carcinogenic process *in vivo*. Since it is impossible to know what level of talc, if any, may actually reach the fallopian tubes and ovaries of a woman exposed to hygienic doses of talc applied in the perineal region, the only recourse an experimentalist has in the design of such a study is to employ as large a dose range as necessary in order to elicit measurable biological perturbations. This describes, in essence, an experimental approach of convenience.

It should now be self-evident that this entire experimental design is fundamentally flawed in several respects, in terms of linking the results of these experiments to talc-induced human ovarian carcinogenesis. First and foremost, lower doses more compatible with a physiologic exposure to talc in the human female reproductive tract were not used in these experiments, even if it were possible to determine what significantly lower dose range that may be. Second, the biological perturbations observed in cultured cells exposed to high doses of talc cannot be reliably extrapolated to such biological responses *in vivo*, which is why animals (typically mice or rats) are used in studies designed to predict the human carcinogenic potential of one or another xenobiotic. Finally, absent the malignant transformation of human cells cultured *in vitro* (utilizing several assays traditionally employed to approximate malignant transformation in this context) following exposure to high doses of talc, the rather non-specific biological responses observed in Dr. Saed’s experiments cannot be interpreted to conclude that talc exposure causes ovarian cancer *in vivo*. At most, the only conclusion that may be reasonably made from these experiments is that exposure to extremely high doses of talc results in the biological perturbation of human cells cultured *in vitro*,<sup>16</sup> a result that is entirely expected based on well-established principles of toxicology. Several of the problematic experimental issues discussed above will be expanded upon below.

**Inadequate Control Experiments:** Dr. Saed’s studies do not adequately address his hypothesis that there is a biological mechanism linking exposure to talc (a hydrated magnesium silicate compound consisting of magnesium, silicon and oxygen – all of which are found at one or another concentration in the human body, and are in fact considered “essential elements”) to ovarian carcinogenesis because Dr. Saed failed to perform additional control experiments designed to test whether other particulate compounds, such as, for example, cornstarch (a powdered carbohydrate derived from the endosperm of corn kernels) or a particulate compound more chemically similar to talc, such as finely ground beach sand (silicon dioxide) produced the same results. Such experiments testing the potential biological effects of other particulate compounds like talc could have been used to determine whether his findings were driven by

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<sup>16</sup> Saed Rep. at 14.

some quality that is unique to talc, or rather its particulate form generally, the characteristics of which are shared by many other compounds.

Specifically, in his investigation, talc was dissolved in DMSO and added to cultured cells as an experimental condition.<sup>17</sup> Changes in the levels of RNA and protein expression in these cells were then measured by qPCR (quantitative polymerase chain reaction) and ELISA (enzyme-linked immunosorbent assay) techniques and compared with levels found in cells treated with DMSO only.<sup>18</sup> Dr. Saed concluded that differences in RNA and protein expression between the talc-treated and DMSO-only-treated samples were evidence of an “oxidative stress” response induced by talc exposure.<sup>19</sup> Overlooked, however, was the possibility that these differences were the result of high-dose particulate exposure generally, and not to talc exposure specifically.

A properly designed experiment would have included a condition(s) where cultured cells were treated with at least one, and preferably several, additional non-talc compounds suspended in DMSO. Such control experiments would help an investigator discern the baseline RNA and protein expression level changes that occur in response to addition of particulate matter generally to cultured cells. Dr. Saed testified that the inclusion of such a condition would have been feasible.<sup>20</sup> He admitted that he did not know whether the addition of an inert substance, such as corn starch, to the cell cultures would have yielded the same RNA and protein expression changes that he observed in talc-treated cell cultures.<sup>21</sup> When confronted with the issue of exclusion of such control experiments, Dr. Saed erroneously concluded that inert substances could not cause a similar oxidative stress response profile because the “untreated” cells exposed to DMSO only “didn’t show that.”<sup>22</sup> The manner in which cultured cells respond to the addition of DMSO alone has no bearing on how they may respond to the addition of DMSO containing a suspended inert particulate substance other than talc.

The failure to include such control experiments to measure potential “oxidative stress responses” to inert particulate substances is a fatal flaw with respect to the veracity of the investigative power of the aforementioned studies to establish a cause and effect relationship between talc exposure and a cellular oxidative stress response. Dr. Saed’s only defense to this fundamentally flawed experimental design was that he “tested several fold.”<sup>23</sup> However, repeating the same flawed experiment several times cannot overcome this underlying methodological flaw.

Dr. Saed’s experiments neither contradict nor support his hypothesis that there is a biological mechanism(s) through which talc may induce an oxidative stress response in cultured human

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<sup>17</sup> Saed Dep. Vol. I 273:10-14.

<sup>18</sup> Saed Rep. at 14-15.

<sup>19</sup> *Id.* at 14-18.

<sup>20</sup> Saed Dep. Vol. I 274:5-9.

<sup>21</sup> *Id.* 273:16-25.

<sup>22</sup> *Id.* 272:20-273:2.

<sup>23</sup> *Id.* 272:14-19.

cells. He merely showed that there are changes in the expression levels of specific RNA and protein molecules that differ between cells treated with DMSO and cells treated with DMSO containing talc. As such, Dr. Saed's studies offer no support for his opinion regarding the biological mechanism by which talc allegedly causes an oxidative stress response in cultured cells *in vitro*, and much further, ovarian carcinogenesis *in vivo*.

**Cell lines:** There are serious methodological concerns with respect to the types of human cells that were used in Dr. Saed's experiments. Four distinct categories of primary cells or established cell lines were used: 1) The EL1 cell line, derived from human spleen and classified as a monocyte/macrophage cell type; 2) "Normal ovarian epithelial" cells – it may be inferred from Dr. Saed's laboratory notebook and the commercial source of these cells (Cell Biologics) that they are "human primary ovarian epithelial cells derived from normal human ovary tissue"; 3) The FT33 cell line, described by the commercial source as "immortalized human fallopian tube epithelial cells"; and 4) Three human ovarian carcinoma cell lines, SK-OV-3, A2780, and TOV-112D, which are, by definition, derived from human ovarian carcinomas.<sup>24</sup> All three of the ovarian carcinoma cell lines are originally from the American Type Culture Collection; the latter two are described as having been derived from endometrioid ovarian adenocarcinomas, and the SK-OV-3 cell line was derived from ovarian carcinoma ascites (histologic subtype unknown).<sup>25</sup>

It is not at all clear why one would conduct experiments related to xenobiotic-induced ovarian carcinogenesis using a cell line (EL1) derived from the monocyte/macrophage lineage, a white blood cell type involved in the adaptive immunity process. It is similarly unclear why one would conduct such experiments using human ovarian carcinoma cell lines (SK-OV-3, A2780, and TOV-112D); if an experimentalist is testing the hypothesis that exposure of human ovarian cells to a potential carcinogen leads to biological effects related to the tumorigenic process, why would cell lines that are derived from ovarian carcinomas represent an appropriate model? These cells, *ipso facto*, represent the ultimate culmination of the tumorigenic process, and would be expected to possess myriad biological and somatic genetic differences compared to "normal" ovarian epithelial cells. Stated simply, the approach of testing a hypothesis as to how cancer may be experimentally induced, *using cancer cells*, is seriously unsound.

## **B. Misinterpretation of Results**

**CA-125 Findings:** Dr. Saed reports an increase in cellular release of the CA-125 protein following talc treatment and claims that this "highlight[s] the implications of the pro-oxidant states caused by talc. . . ."<sup>26</sup> This is a confusing assertion because Dr. Saed does not identify the "implications" that increased CA-125 expression purportedly "highlight[s]." If he intends to suggest that increased CA-125 secretion is suggestive of ovarian carcinogenesis, however, then he misunderstands the clinical use of serum CA-125 protein measurements.<sup>27</sup> The FDA-

<sup>24</sup> Saed Dep. Vol. I, Ex. 1 at SAED000001 (Expert Report Notebook Files).

<sup>25</sup> *Id.*

<sup>26</sup> Saed Rep. at 18.

<sup>27</sup> Notably, in his deposition, Dr. Saed admitted that that he does not know the clinical significance of CA-125. Saed Dep. Vol. I 248:25-250:2.



approved use of measuring serum CA-125 levels is in the context of a “biomarker” to monitor response to ovarian cancer treatment.<sup>28</sup> Although such measurements have also been tested experimentally for decades in an effort to detect ovarian cancer at an early stage, the specificity and sensitivity of serum CA-125 levels in this context are unacceptably low, and the assay is neither useful nor approved for this purpose.<sup>29</sup> Increased serum CA-125 levels have been reported in “benign conditions such as endometriosis, pregnancy, ovulatory cycles, liver diseases and congestive heart failure, as well as in infectious disease such as tuberculosis.”<sup>30</sup> Serum levels of CA-125 are also elevated in non-ovarian cancers, such as “breast cancer, mesothelioma, non-Hodgkin lymphoma, gastric cancer, and leiomyoma and leiomyosarcoma of gastrointestinal origin.”<sup>31</sup> Therefore, any increase in CA-125 levels observed by Dr. Saed is not necessarily indicative of malignant conditions, much less malignant risk. Because increased CA-125 expression can reflect any number of causes, physiologic states, or conditions other than ovarian cancer, its use as a detection tool is highly disfavored and is considered ineffective from a clinical perspective. Nor does it play any role in ovarian cancer causation. Therefore, any effect that exposure to talc may have on cellular release of CA-125 is irrelevant to the question whether it plays any role in causing ovarian cancer.

Some of the utility of CA-125 as a biomarker does stem from the fact that CA-125 secretion can increase with the onset of ovarian cancer. As discussed, however, CA-125 secretion is highly non-specific and increases are more frequently unrelated to ovarian cancer. Furthermore, clinical use of CA-125 as an early detection marker for ovarian cancer is typically accompanied by a transvaginal sonography.<sup>32</sup> Even then, “reports suggest that sensitivity of early stage disease is limited.”<sup>33</sup> If CA-125 is not even a reliable biomarker for the *onset* of ovarian cancer *in vivo*, it is doubtful that CA-125 can be a reliable biomarker for the *increased risk* of onset of ovarian cancer *in vitro*. To the extent that an increase in CA-125 secretion is sometimes associated with ovarian cancer, Dr. Saed still has not shown that CA-125 is a cancer precursor, rather than an effect of such cancer.

These opinions are generally shared by Reviewer #1, who provided a critique of Dr. Saed’s manuscript following submission to *Gynecologic Oncology*. The Reviewer writes that, “The significance of this study would be greatly enhanced if a mouse model corroborated the cell line findings. In this reviewer’s opinion, the cell line studies alone and the increase in CA-125 while intriguing are not sufficiently convincing.”<sup>34</sup>

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<sup>28</sup> Saed Rep. at 18 (citing Jelovac D & Armstrong DK, *Recent progress in the diagnosis and treatment of ovarian cancer*. CA Cancer J Clin. (2011) 61(3):183-203).

<sup>29</sup> See above reference to UKCTOCS clinical trial.

<sup>30</sup> Scholler N & Urban N, *CA125 in Ovarian Cancer*. Biomark Med. (2007) 1(4): 513-523 (internal refs. omitted).

<sup>31</sup> *Id.* at 517 (internal refs. omitted).

<sup>32</sup> *Id.*

<sup>33</sup> *Id.*

<sup>34</sup> Saed Dep. Vol. II, Ex. 35 at 2, Gynecologic Oncology Email dated Sept. 19, 2018 re: GYN-18-1020: Final Decision (“Gynecologic Oncology Decision”).

Finally, the conclusion stated in the Abstract and elsewhere in the manuscript by Fletcher *et al.* (rejected by *Gynecology Oncology* and under review or perhaps in press at *Reproductive Sciences*), stating that, “Talc exposure also resulted in a significant increase in inflammation as determined by increased tumor marker CA-125,” is incorrect and misleading.<sup>35</sup> There was no direct measurement of inflammation in the cultured cells, and a correlation of increased CA-125 secretion with inflammation is speculative at best.

**Cell Proliferation and Apoptosis Findings:** Dr. Saed claims that he has “shown conclusively that talcum powder . . . enhance[s] cell proliferation, and inhibit[s] apoptosis in EOC cells,” as well as in “normal cells, including surface ovarian epithelium, fallopian tube, and macrophages.”<sup>36</sup> At his deposition, he took this claim further, asserting that cell proliferation “is an indirect measure of the beginning of [neoplastic] transformation.”<sup>37</sup> None of this is correct, and Dr. Saed’s attempt to equate cell proliferation with cancer development is profoundly unscientific. As noted above, the lack of appropriate control experiments undermines the specificity of his findings to talc powder, making it impossible to issue such a “conclusive[]” claim. In fact, cell proliferation is a natural response to stress, meaning that this result would be expected to follow many cell treatments *in vitro* and would not remotely be unique to exposure to large doses of talc suspended in DMSO.

In addition, it is unclear why these findings are significant since Dr. Saed testified that there are no studies showing that increased cell proliferation and decreased apoptosis are associated with ovarian cancer risk.<sup>38</sup> The findings also seem irrelevant because Dr. Saed was not aware of any studies showing that these cellular responses are present in any tissue in women who use talc.<sup>39</sup> Nor am I. Regardless, Dr. Saed’s broad characterization of these properties as an “oncogenic phenotype”<sup>40</sup> is not consistent with scientific knowledge.

First, cell proliferation is a regular process in tissue homeostasis, and does not indicate that a normal cell has transformed into a cancer cell. Dr. Saed acknowledged this when he explained that “temporary or initial induction of proliferation [] is a normal response of all normal cells to agents.”<sup>41</sup> Dr. Saed does not explain in his report why his findings are not simply a typical cellular response to the introduction of a foreign agent, such as talc, in cell culture. Furthermore, according to his lab notebooks, the furthest data collection time point in Dr. Saed’s investigation was 72 hours after treatment with talc. At best, Dr. Saed’s study provides a snapshot of the

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<sup>35</sup> Saed Dep. Vol. I, Ex. 7 & 8 at 2 (Fletcher NM, Harper AK, Memaj I, Fan R, Morris RT, Saed GM, *Molecular basis supporting the association of talcum powder use with increased risk of ovarian cancer* (2019) (unpublished manuscript)) (“Manuscript”) at 2.

<sup>36</sup> Saed Rep. at 16.

<sup>37</sup> Saed Dep. Vol. II 464:2-11.

<sup>38</sup> Saed Dep. Vol. I 268:4-269:4.

<sup>39</sup> *Id.* 268:25-269:4.

<sup>40</sup> Saed Rep. at 17.

<sup>41</sup> Saed Dep. Vol. I 265:10-15.

initial reaction of cells to particulate exposure. It is unreasonable to extrapolate from these findings that cells are therefore “oncogenic” and any observed fluctuations in proliferation and apoptosis are permanent. Dr. Saed’s findings on proliferation and apoptosis do not seem to have any bearing on whether talc increases the risk of ovarian cancer.

### C. Limitations of Results and the Need for Further Study

**Alterations in Expression Levels and Activities of the Enzymes Studied Do Not Equate to an Altered State of Oxidative Stress in the Cultured Cells:** As described in much of the evidence submitted by Dr. Saed in the context of expert testimony, including laboratory notebooks, the transcript of his deposition, and perhaps most succinctly, the manuscript by Fletcher *et al.* summarizing his findings, he consistently states and otherwise implies, many times, that decreased expression and activity of the antioxidant enzymes CAT and SOD3, increased expression and activity of the pro-oxidants iNOS, NO<sub>2</sub>-/NO<sub>3</sub>-, and MPO, and decreased expression and activity of antioxidant enzymes GSR and GPX “enhances the pro-oxidant state in . . . cells.”<sup>42</sup> While he reports RNA levels (“expression”) of these enzymes, as measured by qPCR, that are altered (up or down) following exposure to talc for 72 hours, he frequently conflates “expression and activity” of these enzymes as assessed by an ELISA, which measures protein levels.<sup>43</sup> The reactions that these enzymes catalyze may alter the levels of reactive oxygen species (typically nitrogen- or oxygen-based), but these reactive oxygen species are very unstable and cannot be measured by an ELISA. As best as I can tell from his laboratory notebooks, and from the content of the manuscript, he is using protein levels, as measured by an ELISA, to estimate the amount of enzymatic activity that a certain quantity of protein may have. This is an indirect and misleading presentation of the data. *Regardless*, none of these data are indicative of an increased pro-oxidant state in the cultured cells *in vitro*, much less *in vivo*.

**The Single Nucleotide Polymorphism (SNP) Findings are Vague and of Questionable Relevance:** *First*, Dr. Saed has not established that his findings actually represent mutations, as he claims in his manuscript. In Table 2, he lists what he believes to be talc-induced genetic mutations resulting in SNP genotype switches in “key redox enzymes.”<sup>44</sup> But as he acknowledged at his deposition, he was not “able to estimate the volume of cells that this genotype switch occurred in.”<sup>45</sup> Rather, his technique only reports whether there is a “population of cells that acquired th[e] genotype” at issue.<sup>46</sup> This limitation is significant because it cannot rule out the possibility that the cells under treatment had one of three possible SNP genotypes (heterozygous, homozygous for minor allele, or homozygous for major allele) already, prior to treatment – in other words, that Dr. Saed was not finding treatment-induced mutations at all, but

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<sup>42</sup> Manuscript at 2.

<sup>43</sup> *Id.* at 20-22 (panels A and B of each figure show RNA expression, while panels C and D of each figure show protein levels as measured by ELISA).

<sup>44</sup> *Id.* at 19 (Table 2).

<sup>45</sup> Saed Dep. Vol. I 198:13-199:15.

<sup>46</sup> *Id.*

rather preexisting genetic variability that became manifest after the expansion of one or another subpopulation of cells in culture as a result of variable proliferation of a heterogeneous cell population. Indeed, the term “single nucleotide polymorphism” is by definition a type of genetic variation that exists in a population at a particular nucleotide position in a particular gene. In other words, polymorphisms represent naturally occurring genetic variants, not “mutations”, at least in the context of putative carcinogen-induced mutagenesis over a 72-hour period. This occurs when a specific nucleotide in a specific gene is variable throughout a population, occurring when one genetic variant is inherited from one parent and the other genetic variant is inherited from the other parent. At a typical SNP site in the human genome, an individual may be homozygous for the SNP (for example T/T or C/C), or heterozygous for the SNP (C/T). These are not mutations. They represent the genetic basis of human phenotypic variation, and one may find SNPs in the great majority of human genes. This well-established genetic phenomenon throws Saed’s entire claim of talc-induced mutations into doubt.

**Second**, none of the SNPs identified by Dr. Saed in his background discussion of ovarian cancer-associated polymorphisms was observed in his talc study. Dr. Saed broadly states in his report that SNPs in genes that code for certain enzymes (such as *CAT*, *GPX1*, *GSR* and *SOD2*) have been associated with increased ovarian cancer risk.<sup>47</sup> In making this statement, Dr. Saed relies, in part, on the Belotte study, conducted in his lab, which actually found an association between a specific SNP in the *CAT* gene and ovarian cancer **survival**, not risk. Dr. Saed fails to elaborate on his statement and only identifies three SNPs in redox genes that he claims are related to ovarian cancer risk: rs1001179 (reducing *CAT* activity), rs4673 (reducing *CYBA* activity) and rs2333227 (occurring in the *MPO* gene).<sup>48</sup> The rs1001179 polymorphism is actually associated with ovarian cancer survival, not risk.<sup>49</sup> And a meta-analysis of 43 case-control studies involving various types of cancer found no association between the rs2333227 polymorphism (*MPO*) and an increased cancer risk.<sup>50</sup> Regardless, none of the underlying studies referenced by Dr. Saed is a genome-wide association study (GWAS) that examined the prevalence of a given SNP in a larger population of ovarian cancer patients. In other words, even if these three SNPs were hypothesized to be associated with ovarian cancer risk in isolated, statistically-underpowered investigations, their significance when it comes to the broader questions of ovarian cancer risk in the general population has not been established.

Perhaps recognizing this gap in his analysis, Dr. Saed also lists a number of additional SNPs identified by GWAS that influence ovarian cancer risk.<sup>51</sup> It is unclear whether these polymorphic variants are associated with an increased or decreased risk. None of the variants

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<sup>47</sup> Saed Rep. at 7-8.

<sup>48</sup> *Id.* at 8.

<sup>49</sup> Belotte J et al., *A single nucleotide polymorphism in catalase is strongly associated with ovarian cancer survival*. PLoS One. (2015) 24:10(8):e0135739.

<sup>50</sup> Chu H et al., *The MPO –463G>A polymorphism and cancer risk: a meta-analysis based on 43 case-control studies*. Mutagenesis. (2010) 25(4):389-95.

<sup>51</sup> Saed Rep. at 8.

seem to occur in protein-coding regions except possibly rs2072590, which is “located at 2q31” within “a family of *HOX* genes.”<sup>52</sup> The remaining variants occur “near” *BNC2* and *MERIT40*, “downstream” of *MYC*, and “intronic” to *SKAP1* and *TIPARP*.<sup>53</sup> At most, these SNPs could theoretically function to regulate the expression of genes, but not functions of the encoded protein, if they have any effect at all. It is certainly far from evident that any of these genes is involved in the redox state of cells.

**Third**, none of the “mutations” that Dr. Saed observed in his talc-treated cells has been reported by GWAS to be associated with an increased ovarian cancer risk. It should be noted that many SNPs are “silent,” in that they do not result in any change in activity by the protein, and Dr. Saed has failed to show that the SNPs he claims resulted from talc-induced genotype switching are related to altered functions of the genes under study. Dr. Saed lists *CAT* (rs769217), *NOS2* (rs2297518), *GSR* (rs2448), *GPX1* (rs2448) and *SOD3* (rs2536512) genetic variations in Table 2 of his manuscript.<sup>54</sup> He was unable to state whether these SNPs have been reported to occur in women using talc.<sup>55</sup> And as discussed below, the observed “mutations” in *CAT*, *NOS2*, and *GPX1* fail to support his conclusions, for a number of additional reasons. Notably, the *GSR* and *SOD3* genes were not affected at all by talc treatment, as reported in Table 2.

*CAT* (rs769217) SNP. Dr. Saed did not observe this “mutation” in A2780 and SK-OV-3 cell lines. If this mutation is the mechanism by which talc allegedly increases ovarian cancer risk, it is unclear why the mutation is not commonly seen across all talc-treated cells. Dr. Saed makes many logical leaps to connect this genetic variant to an elevated cancer risk.

First, Dr. Saed states that the SNP results in an isoleucine to threonine amino acid change, but no more information is provided as to how or whether this change affects protein function.<sup>56</sup> Does the mutation alter the catalytic site of the enzyme? Does it affect secondary and tertiary structures of the protein or modify its interactions with other molecules? Dr. Saed’s only observation is that talc-treated cells exhibit decreased *CAT* expression and catalase activity. However, he acknowledges in his report that these changes may be caused by other mutations in *CAT*, and not the rs769217 variant itself.<sup>57</sup> In fact, it would be much more logical to conclude that lower amounts of *CAT* protein in a cell would result in lower *CAT* activity (converting hydrogen peroxide to water and oxygen). Nevertheless, there are many straight-forward follow-up experiments that Dr. Saed could have conducted to understand the specific effect of the rs769217 genetic variant on catalase activity (if any). Scientists regularly create cell lines with targeted mutations through the use of genetic editing tools (such as CRISPR/Cas9), to study the impact of specific genetic mutations on protein functions. Dr. Saed could have repeated his

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<sup>52</sup> *Id.*

<sup>53</sup> *Id.*

<sup>54</sup> Manuscript at 19 (Table 2).

<sup>55</sup> Saed Dep. Vol. I 225:17-226:3.

<sup>56</sup> Manuscript at 19.

<sup>57</sup> Saed Rep. at 18.



ELISA assays and done pull-downs of the catalase protein in normal cells and cells with targeted mutations to understand whether and how the rs769217 mutation affected the catalase function and its interaction with other molecules (including its function as a tetramer). Only with these sorts of follow-up experiments could Dr. Saed actually attribute a causal relationship between this specific genetic variant and the protein activity observed.

The minor allelic frequency (MAF) of the rs769217 SNP was described as 12.3%.<sup>58</sup> As presented, this figure can only be derived from the genotypes of large numbers of individuals in a population. For a single individual, the MAF would by necessity be 0, 50%, or 100%. These are basic principles of human genetics. In the talc treatment experiments, data are presented as Allele 1 and Allele 2 scores with and without talc treatment; in the case of TOV-112D cells, for example, the C/C genotype at rs769217 becomes C/T following talc treatment with scores of Allele Amp Scores of 0.67 and 0.88.<sup>59</sup> Although it is not clear exactly what these scores represent (the total is greater than 1.0), it may be assumed that a substantial proportion of the cells exposed to a dose of talc for 72 hours sustained a C to T mutation. I have never witnessed such potent mutagenesis by any agent – especially within a narrow 72-hour post-treatment window. Dr. Saed was similarly unable to recall any agent that has produced such rapid, robust mutagenesis.<sup>60</sup> It is highly unlikely that the increased MAF is due to genotoxicity that is unique to talc, considering a previous study found that talc was not genotoxic.<sup>61</sup> Rather, the high MAF is likely the result of general genotoxicity associated with the introduction of extremely high dosages of foreign particulate into cell cultures, the selective expansion of small numbers of cells present in culture with the MAF, otherwise undetectable, as the cells were induced to proliferate by talc exposure, some sort of experimental error, or all of the above. The inclusion of appropriate control experiments (as previously described) could have shed light on these questions. Finally, as noted elsewhere in this report, the allele frequencies for all the studied SNPs should have been presented in a quantitative fashion, rather than qualitative. For a mutation to be “fixed” in an affected cell, the cell must obviously undergo division to two daughter cells. That specific SNP sites that happened to be associated with enzyme activity of the “critical” genes under study underwent qualitative mutagenesis from one nucleotide to another in 100% of the talc-treated cells, in 72 hours, is not only implausible, it is *impossible*, in light of the doubling time of proliferating cells.

SOD3 (rs2536512) and GSR (rs8190955) mutations. Dr. Saed’s report states that these “SNP genotypes were not detected in any cell line.”<sup>62</sup> Part B of Table 2 confirms that neither the control nor talc-treated cell lines had mutations at these locations.<sup>63</sup> However, the first part of

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<sup>58</sup> Saed Dep. Vol. I, Ex. 1 at SAED000078.

<sup>59</sup> *Id.* at SAED000080.

<sup>60</sup> Saed Dep. Vol. I 252:3-7.

<sup>61</sup> Endo-Capron S et al., *In vitro response of rat pleural mesothelial cells to talc samples in genotoxicity assays (sister chromatid exchanges and DNA repair)*. *Toxicol In Vitro*. (1993) 7(1):7-14.

<sup>62</sup> Saed Rep. at 18; Manuscript at 11.

<sup>63</sup> Manuscript at 19.

the table still lists the MAF of mutations as 19.1% and 47.6%, respectively.<sup>64</sup> As for the CAT gene data above, it is unclear from whence the MAF data are derived. Is it a calculation of allelic frequency based on the total pooled alleles from all of the talc-treated cells? Is it an average of the MAF values calculated individually for each of the talc-treated cell lines? Is it the naturally-occurring frequency of the mutation in the general population? If it does refer to the frequency in the general population, what proportion of cells treated with talc actually displayed these mutations?

Regardless of how the MAF data were calculated, if no SNP genotypes were detected in the cell lines, how can these *SOD3* and *GSR* mutations still be attributed to changes in redox activity and provide any basis for Dr. Saed's theory that talc exposure leads to mutations associated with an increase in ovarian cancer risk?

*NOS2* (rs2297518) mutation. The concerns described above also apply to the *NOS2* mutation. This mutation was not found in the talc-treated A2780 or TOV-112D cell lines, had a MAF of 17.3% and resulted in a serine to leucine amino acid change.<sup>65</sup> No additional studies were conducted to confirm that observed increases in protein activity were actually caused by the rs2297518 mutation.

*GPXI* (rs3448) mutation. In addition to the concerns described above, other issues also undermine the significance of the *GPXI* findings. First, Dr. Saed focuses on the mutation because the "acquisition of chemoresistance by ovarian cancer cells is associated with a switch from *GPXI* SNP genotype to the normal *GPXI* genotype."<sup>66</sup> It is unclear how any chemoresistance finding in already cancerous cells is relevant to understanding whether an association exists between talc exposure and ovarian cancer risk. Among genes coding for glutathione peroxidase enzymes, only the rs6456822 SNP in *GPX6* has been reported as having a genome-wide significance for association with serous epithelial ovarian cancer risk.<sup>67</sup> Simply put, Dr. Saed does not provide any basis for why the rs3448 genetic variant is associated with ovarian cancer risk.

Dr. Saed did not observe the *GPXI* conversion in one of the normal cell lines (HOSEpiC) after exposure to talc. As with the *CAT* mutation, if this mutation is the mechanism by which talc allegedly increases ovarian cancer risk, it is unclear why the mutation did not occur in all normal cells treated with talc. Showing this mutation occurs in all normal cells treated with talc would be the first step toward understanding any biological mechanism whereby talc allegedly leads to an increased risk of ovarian cancer.

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<sup>64</sup> *Id.*

<sup>65</sup> *Id.*

<sup>66</sup> Saed Rep. at 19.

<sup>67</sup> Kuchenbaecker KB et al., *Identification of six new susceptibility loci for invasive epithelial ovarian cancer*, Nat Genet. (2015) 47(2):164-71.

Finally, Dr. Saed describes the amino acid changes and effect on protein activity for the *GPXI* mutation as “unknown.”<sup>68</sup> Dr. Saed has no idea why the mutation is significant to his opinion on talc and ovarian cancer risk other than the fact that the mutation occurs in a gene involved in redox activity. The mere existence or creation of a mutation is not necessarily biologically significant. For example, the SNP could be a synonymous mutation that does not result in any amino acid change in the resulting protein and has no consequence on glutathione peroxidase enzyme function. If the SNP did result in an amino acid change, the change could be inconsequential because it does not affect the activity of the enzyme, the secondary or tertiary structures of the protein or how the protein interacts with other molecules. As it stands, there is no basis for the relevance of the *GPXI* mutation in studying ovarian cancer risk.

My interpretation of the experimental design and presentation of data related to the measurement of SNP genotypes in several genes involved in the general oxidative state of the cell, after exposure to talc, is that Dr. Saed has conflated mutagenesis with normal genetic variation, especially as the latter may exist in a highly heterogeneous state in cells cultured *in vitro*. It is not at all clear how these data bear on the purported risk of talc for the development of ovarian cancer. This view would seem to be shared by Reviewer #1 of the manuscript submitted to *Gynecologic Oncology*, who writes, “The significance of SNP alterations should be further clarified.”<sup>69</sup>

If Dr. Saed had been interested in demonstrating that talc was indeed mutagenic (creating mutations) in his cell lines, the most appropriate experiments would have examined global mutagenesis in a much broader context. One potential experiment would involve comparing talc-treated cells to untreated cells with respect to potential mutations generated throughout the entire exome (coding region of the genome). This experiment would have involved extraction of DNA from treated vs. untreated cells, followed by sequencing of the entire exomes of these cells using next-generation DNA sequencing technology. This technology is typically available in core facilities of most research universities and academic medical/cancer centers, and if not, is readily performed by myriad commercial laboratories for a modest cost. An alternative approach would have been to perform next-generation DNA sequencing analysis of a panel of several hundred genes known to be involved (“driver genes”) in carcinogenesis when mutated. Such analyses are also performed by many commercial laboratories.

In summarizing my conclusions on scientific clarity and relevance of the SNP studies, I can only conclude that the rationale of studying talc-induced mutagenesis occurring *exclusively* at SNP sites in some of the genes encoding enzymes under study, including the anti-oxidant enzymes CAT, GSR, GPX1, and SOD3, and the pro-oxidant enzyme NOS2, appears to represent a chain of logic by Dr. Saed that would correlate talc-induced mutations at these specific sites with altered enzymatic activity of the encoded proteins, followed by increased oxidative stress in the affected cells; this complex theoretical sequence of talc-induced events in cultured cells would appear to tie all of his various hypotheses together. Parenthetically, there is no evidence or

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<sup>68</sup> Manuscript at 19.

<sup>69</sup> Gynecologic Oncology Decision at 2.

suggestion provided in Dr. Saed's manuscript as to how the enzymes affected by talc exposure (expression levels) were so affected if they ***did not contain SNPs subject to mutagenesis*** and thus not studied at all (*MPO*), or ***did*** contain SNPs of purported functional consequence but ***did not sustain mutagenesis by talc*** (*GSR* and *SOD3*). These data are presented in Table 2 of Dr. Saed's manuscript. In my expert opinion, this experimental design and interpretation of results are deeply flawed, naïve, and the results regarding qualitative (as opposed to quantitative) mutagenesis at specific SNP sites are, candidly, very difficult to believe. I have expanded upon all the critical elements of this paragraph elsewhere throughout this Expert Report.

**Limitations of Studies *in vitro*:** Even if Dr. Saed's research methodology were flawless, and his conclusions unassailable, his studies *in vitro* would not establish a mechanism of carcinogenesis *in vivo*. The most even Dr. Saed claims to have actually shown with his experiment is a change in the levels of RNAs and proteins that encode certain proteins, changes in the activities of some of these proteins (by inference), an increase in cell proliferation and a decrease in apoptosis in response to talc exposure; but there is an enormous gap between such findings in a petri dish and proving that a particular agent is actually a probable cause of ovarian cancer.

Indeed, as a general rule, a study *in vitro* cannot, by itself, support conclusions about anything that happens in actual animal or human tissues. At most, careful studies *in vitro* may generate hypotheses that may be tested with follow-up studies using models *in vivo*, e.g., animals. The comments on Dr. Saed's manuscript reflect this principle. According to Dr. Saed's deposition testimony, *Gynecologic Oncology*<sup>70</sup> declined to publish his paper, and a reviewer explained that he "needed to do *in vivo* . . . animal experiments."<sup>71</sup> I note, too, that Dr. Saed volunteered at his own deposition that, in order to determine whether his experiments truly emulated chronic inflammation in humans, he would "have to do animal studies."<sup>72</sup>

The need for studies *in vivo* to evaluate Dr. Saed's results *in vitro* is especially glaring here, because previous work *in vivo* on the relationship between talc and ovarian cancer tends to refute, rather than support, Dr. Saed's conclusions. I am not aware of any research *in vivo* specifically addressing the effects of talcum powder exposure on oxidant and anti-oxidant enzymes and resultant oxidative stress in human cells. Two animal studies, however, have shown no increase in ovarian cancer development following talcum powder treatment. Hamilton, *et al.*, injected rats with mega-doses of talc adjacent to the ovaries, and reported no inflammation or neoplasia.<sup>73</sup> Keskin, *et al.*, exposed rats to talc either intra-vaginally or on the perineum. While certain infections developed (likely because the talc was not sterile), there was

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<sup>70</sup> Dr. Saed testified that he submitted his manuscript to a journal called "*OB-GYN Oncology*." I am aware of no journal with that name, and subsequent document productions from Dr. Saed make clear that he intended to refer to *Gynecologic Oncology*.

<sup>71</sup> Saed Dep. Vol. I 46:22-47:2; *see also* Gynecologic Oncology Decision.

<sup>72</sup> Saed Dep. Vol. II 542:16-25.

<sup>73</sup> Hamilton TC et al., *Effects of talc on the rat ovary*. Br J Exp Pathol. (1984) 65(1):101-6.

no neoplastic change in any of the exposed animals.<sup>74</sup> Dr. Saed is capable of performing studies *in vivo* to challenge these conclusions, but said at his deposition that he lacks the time and the money for it.<sup>75</sup> In light of the data from earlier studies, I am skeptical that Dr. Saed's findings could be replicated *in vivo*, and without such replication, they are insufficient to reliably suggest the carcinogenic mechanism that he proposes.

Relatedly, Dr. Saed is presupposing that talc can travel to the fallopian tubes or ovaries and cause inflammation there, but his *in vitro* experiments obviously cannot evaluate that assumption, and support from existing research is lacking. In fact, Dr. Saed's suggestion that it is widely accepted that talc applied to a woman's underwear will travel to her ovaries against gravity<sup>76</sup> and that studies of sperm are somehow relevant to this question<sup>77</sup> ignores fundamental anatomy. Notably, the often-cited study regarding the presence of talc in ovarian tissue of women with ovarian cancer discovered talc both in women who reported perineal talc use and women who did not, suggesting that the talc came from a different source.<sup>78</sup>

With respect to Dr. Saed's assertion that his data support a role for oxidative stress (presumably produced by talc exposure) in ovarian carcinogenesis, in addition to my concerns raised in this report, both Reviewers for *Gynecologic Oncology* commented on this assertion specifically as it was articulated in Dr. Saed's manuscript.<sup>79</sup> Reviewer #1 writes, "The first bulleted highlight [the Journal requires a list of bulleted highlights of research papers submitted for publication], 'Oxidative stress is a key mechanism to the initiation and progression of ovarian cancer' is not supported by this investigation and should be omitted."<sup>80</sup> Reviewer #2 writes, "While changes in redox potential play an important role in in tumor biology in general, the present data are insufficient to back up the claim that talcum is central to the development of ovarian cancer."<sup>81</sup>

Finally, Dr. Saed appears to take for granted that ovarian cancer is caused by inflammation, but this, too, has not been established. Dr. Saed essentially ignores the body of science suggesting that chronic inflammation does not play a role in the development of ovarian cancer,<sup>82</sup> as well as

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<sup>74</sup> Keskin N et al., *Does long-term talc exposure have a carcinogenic effect on the female genital system of rats? An experimental pilot study*. Arch Gynecol Obstet. (2009) 280(6):925-31.

<sup>75</sup> Saed Dep. Vol. I 50:10-13.

<sup>76</sup> Manuscript at 8.

<sup>77</sup> *Id.* (citing Kunz G et al., *The uterine peristaltic pump. Normal and impeded sperm transport within the female genital tract*. Adv Exp Med Biol. (1997) 424:267-77; Leyendecker G et al., *Uterine peristaltic activity and the development of endometriosis*. Ann NY Acad Sci. (2004) 1034:338-55; Zervomanolakis I et al., *Physiology of upward transport in the human female genital tract*. Ann NY Acad Sci. (2007) 1101:1-20

<sup>78</sup> Heller et al., *The relationship between perineal cosmetic talc usage and ovarian talc particle burden*. Am J Obstet Gynecol. (1996) 174(5):1507-10.

<sup>79</sup> Gynecologic Oncology Decision at 2-3.

<sup>80</sup> *Id.* at 2.

<sup>81</sup> *Id.*

<sup>82</sup> Malmberg K et al., *Serous tubal intraepithelial carcinoma, chronic fallopian tube injury, and serous carcinoma development*. Virchows Arch. (2016) 468(6):707-13; Rasmussen et al., *Pelvic inflammatory disease and the risk* (cont'd)



studies that considered whether aspirin use and anti-inflammatory drugs reduced the risk of ovarian cancer,<sup>83</sup> with mixed results. As the Malmberg study concluded after finding no significant correlation between histological signs of inflammation and serous ovarian cancer, “Additional studies are needed to further evaluate the role of inflammation in carcinogenesis in the fallopian tube and its clinical implications of preventing serous carcinoma.”<sup>84</sup>

**Need for Further Study:** In addition to the concerns noted above regarding the limitations of the studies performed *in vitro*, and the inappropriate conclusions drawn from them, several related types of studies were notably *not* performed by Dr. Saed in the context of providing evidence central to the fundamental assertion of plaintiffs that perineal talc use causes ovarian cancer. It is widely accepted in the cancer research community that there are several relatively straightforward assays that may be used to support the hypothesis that “normal” cells cultured *in vitro* have been stimulated by some type of exposure or manipulation (talc treatment in this case) to progress toward, or to fully develop, a neoplastic phenotype. These assays include, but are not limited to, the assessment of loss of contact inhibition by cells cultured in a petri dish *in vitro*, the acquisition of anchorage independent growth potential (as assessed by culturing cells in suspension in soft agar), and perhaps the most compelling experiment, demonstrating that the treated cells have obtained neoplastic potential as assessed by their ability to form tumors following subcutaneous injection into athymic (“nude”) mice. All these assays employ standard, well-established methodologies, and could have been readily performed by Dr. Saed using the “normal” cell lines described in his studies. As discussed earlier, none of these studies could have been performed using the three ovarian carcinoma cell lines described, however, since they have already undergone neoplastic transformation (in the humans from whence these cancers arose, and from whence the cell lines were derived). Notably, the three ovarian carcinoma cell lines could have been used as positive controls for the three assays described above, as they would have certainly demonstrated loss of contact inhibition in a petri dish, anchorage independent growth in soft agar, and tumorigenicity in athymic mice. I note that Dr. Saed himself proposed to do the second assay just mentioned involving suspension in soft agar, even stating in his proposal that actually demonstrating “neoplastic transformation” would be “critical in establishing a cause and effect relationship” between talc exposure and ovarian cancer,<sup>85</sup> but as he confirmed at his deposition, he never performed such a study.<sup>86</sup>

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of ovarian cancer and borderline ovarian tumors: A pooled analysis of 13 case-control studies. *Am J Epidemiol.* (2017) 185(1): 8–20; Zhou et al., *Pelvic inflammatory disease and the risk of ovarian cancer: a meta-analysis.* *Cancer Causes Control.* (2017) 28(5):415-28.

<sup>83</sup> Ni X et al., *Meta-analysis on the association between non-steroidal anti-inflammatory drug use and ovarian cancer.* *Br J Clin Pharmacol.* (Jan. 2013) 75(1):26-35.

<sup>84</sup> Malmberg et al. (2016) at 712.

<sup>85</sup> Saed Dep. Vol. II, Ex. 44 at 3, *The Role of Talc Powder Exposure in Ovarian Cancer: A Mechanistic Approach.*

<sup>86</sup> Saed Dep. Vol. II 513:6-14.

**D. Concerns Regarding Data and Handling/Manipulation of Laboratory Notebooks Generally**

I have carefully studied three PDF files (in color) representing scanned portions of laboratory notebooks pertaining to the studies discussed in this Expert Report, that were provided by Dr. Saed, as well as Dr. Saed's deposition testimony about the conduct of his studies. My understanding is that the three PDF files accurately reflect the contents of some portion of the laboratory notebooks related to the studies discussed herein, and that the content of the notebooks was produced by Dr. Saed or members of the Saed laboratory working under his supervision. As a result of miscalculations, changing of dates on particular pages, whiting-out of data or notes, addition of data or notes to certain pages on different dates, the taping of data sheets cut from another source over data or notes previously existing on certain pages, the presence of data and other information in these notebooks that contradict Dr. Saed's statements during deposition as well as data and conclusions reached in the manuscript describing these studies that were submitted to at least two biomedical journals, and other irregularities too numerous to describe in detail, I have reached the following conclusions: 1) Some of the data and handwritten notes in these notebooks were intentionally manipulated; 2) Some of the data in these notebooks were selectively excluded from the final conclusions ultimately manifest in the manuscript submitted for publication; 3) Some of the data in these notebooks and conclusions drawn from them are internally inconsistent; 4) The handling of these laboratory notebooks and the recording of data and notes therein are egregiously inconsistent with the very minimum of well-accepted standard operating procedures with respect to the handling of laboratory notebooks and the recording of data and notes in the context of laboratory research; and, 5) *It is my expert (as defined on pages 2 and 3 of this Report) opinion that some of the data in these notebooks are at the very least unreliable, and at worst fabricated, and that the conclusions drawn from these data, as a whole, are thus unbelievable and essentially worthless with respect to the written and stated claims relating to a possible mechanism(s) through which talc may induce tumorigenesis in cultured cells specifically, and by multiple layers of illogical extension, through which talc may induce ovarian cancer in women exposed to talc generally.*

For the record, I received three notebook files. The first ("Expert Report Notebook Files") was described as the laboratory notebook that relates to Dr. Saed's work for his expert report. It consists of 97 pages (with what would appear to be printed stickers in the bottom corner of each page labeled SAED000001(color) – SAED000097(color)). There are handwritten numbers on the bottom corner of each page, beginning with "30" on page 1 and "124" on page 97. There are two un-numbered pages inserted between the handwritten pages 33 and 35, and one un-numbered page inserted between the handwritten pages 39 and 40, possibly accounting for the discrepancy of two "missing" pages with respect to the handwritten numbered version. For orientation, page 1 (or 30) contains color photographs of the front and back of a commercial container of "Johnson's baby powder."

The second laboratory notebook file ("Abstract Lab Notebook Files") contains a table of contents on the un-numbered first page, with a series of dates, 9/26/2017 – 10/20/2017, descending vertically on the left side, and page numbers from 38-63 descending vertically on the right side. The pages are hand-numbered in the bottom corner, beginning with 38 after the TOC

page and ending with 61, prior to the last page consisting of a scientific poster prepared for presentation.

The third laboratory notebook file (“Preliminary Work Notebook Files”) represents the first 30 pages that are missing from the Expert Report Notebook Files. My understanding is that plaintiffs did not originally share it with defendants because they characterized it as containing only preliminary work.<sup>87</sup> It begins with a table of contents on the un-numbered first page, with a series of dates, 10/15/2017 – 10/6/2017, descending vertically on the left side, and page numbers from 1-124 descending vertically on the right side. Pages 25-30 are missing from the table of contents. The pages are hand-numbered in the bottom corner, beginning with 1 after the TOC page containing a photograph of a container of “Talc” from Fisher Chemical. The next page is un-numbered and contains the same color photographs of a commercial container of “Johnson’s baby powder” that appeared in the Expert Report Notebook Files. The next page is numbered 2 and the rest are numbered consecutively 3-24.

Examples of some of the irregularities described in the first paragraph of section IV.D of this Expert Report (above) include:

1) Pages from another source taped onto the laboratory notebook page, white-out present in both files, including dates whited out and single entries that are made with ink of a different color than the text otherwise filling the same page. I further note that apparent manipulation of the dates has resulted not only in lab books that have entries out of chronological order, but also statements that cannot possibly be true. For example, page 25 of the Expert Report Notebook Files is dated January 7, 2018, and claims to be recording protein extractions from samples 356 to 386.<sup>88</sup> The first line after the top of this page states that the cells were seeded on January 3, 2018.<sup>89</sup> The very next page identifies samples 356 through 386.<sup>90</sup> But exactly the same samples are also identified on page 20 of the Preliminary Work Notebook Files (which, as I note above, plaintiffs initially withheld from production on the ground that it was unrelated work). *That* page refers to the actual seeding of the samples and is dated *February 1, 2018* – or *nearly a month after* protein extractions were supposedly taken from the same samples (which had not been created yet).<sup>91</sup> There is no question that these pages in the separate parts of the Notebooks are referring to the same samples – Dr. Saed said so himself at his deposition, calling the samples “exactly the same.”<sup>92</sup> In fact, the February 1 date in the Preliminary Work Notebook Files follows a “1/3” date that has been crossed out<sup>93</sup> – a date that matched the date referred to on page

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<sup>87</sup> Saed Dep. Vol. I 13:18-14:10, 15:24-16:1.

<sup>88</sup> Saed Dep. Vol. I, Ex. 1 at SAED000025(color).

<sup>89</sup> *Id.*

<sup>90</sup> *Id.* at SAED000026(color).

<sup>91</sup> Saed Dep. Vol. II, Ex. 23 at Ghassan Saed’s Talc Study Lab Notebook – Preliminary Study (“Preliminary Work Notebook Files”) at 20.

<sup>92</sup> Saed Dep. Vol. II 390:7-17.

<sup>93</sup> Preliminary Work Notebook Files at 20.

25 of the Expert Report Notebook Files<sup>94</sup> as the date when the cells were supposedly seeded. These changes suggest that the dates were intentionally manipulated (rather than, for example, that the author mistakenly believed that it was January 3 on February 1).

2) Throughout the Preliminary Work Notebook Files, the handwritten page numbers are invariably smudged, suggesting either erasure and writing over, or white-out and writing over.

3) On page 19 of the Preliminary Work Notebook Files, there is a handwritten entry as follows: “1/31/18 – The presence of 1000 µg/ml is physically killing the cells. – We need to decrease dose.”<sup>95</sup> In none of the pages preceding page 19 of the Preliminary Work Notebook Files, or in any section of the Abstract Lab Notebook Files (containing experiments ostensibly performed prior to 1/31/18), is there evidence of such toxicity. In fact, data related to gene expression (as assessed by RNA levels) are readily obtained at doses of 20, 100 and 1000 µg/ml. In some cases, gene expression of particular enzymes is higher at 1000 µg/ml than at 20 or 100 µg/ml, inconsistent with cells being “physically killed” at 1000 µg/ml. In addition, the amount of RNA obtained from a given number of cells is similar in control vs. treated cells, and from cells treated at various doses (20 – 1000 µg/ml). These data are also inconsistent with a greater proportion of “dead” cells at 1000 µg/ml. What is *clearly* apparent, however, is that gene expression and CA-125 secretion levels at a dose of 1000 µg/ml do not follow a traditional “dose-response” (a biological response becoming increasingly higher or lower in response to an increasing dose of test substance). In quantitating CA-125 secretion, for example, sometimes the amount does not change with talc, sometimes it is lower with talc, and sometimes it is higher with talc, compared to DMSO control treatment of the same cells.<sup>96</sup> This phenomenon does not fit with a central tenet of Dr. Saed’s conclusion, which is that there is a clear dose-dependent response in terms of gene expression, protein “activity,” CA-125 secretion, etc., following talc exposure. This selective exclusion of data in order to fit data to a particular hypothesis or conclusion, “cherry-picking” data to use a colloquialism, is unsound scientific methodology of the highest order.

4) With respect to data points themselves, there is clear evidence of error (human or machine) in terms of simple arithmetic calculations. For example, in a random spot check (by me) of raw data in the Expert Report Lab Notebook Files, consider the computer-generated table (whether populated by a human or a machine being impossible to know) on page SAED000033(color). These data relate to an ELISA-based measurement of catalase “protein/activity” following exposure of cultured cells to talc at doses of only 5, 20 and 100 µg, (presumably per ml?) and the table is dated 1/11/18.<sup>97</sup> This date is 20 days before 1/31/18, the date upon which, in the

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<sup>94</sup> Saed Dep. Vol. I, Ex. 1 at SAED000025(color).

<sup>95</sup> Preliminary Work Notebook Files at 19.

<sup>96</sup> For example, see Preliminary Work Notebook Files at 13.

<sup>97</sup> Saed Dep. Vol. I, Ex. 1 at SAED000033(color).

Preliminary Work Notebook Files, a notation is found that, “The presence of 1000 µg/ml is physically killing the cells...”<sup>98</sup>

Regardless, if one considers the data table in question, the first horizontal row concludes on the far right with an “Average” value of 11.07 for three replicate values of 9.98, 11.63, and 10.50.<sup>99</sup> The correct average would have been 10.70. In horizontal line two of the same table, the “Average” value is listed as 9.13 for three replicate values of 9.18, 10.64, and 9.09.<sup>100</sup> The correct average would have been 9.64. Thus, the recorded difference between “control” A2780 cells and talc-treated (5 µg) A2780 cells is 1.94 nmol/min/ml<sup>101</sup>; the actual difference is 1.06 nmol/min/ml, a much smaller difference. A “larger difference” in this case would have been more consistent with the experimental hypothesis and conclusions, which of course could be simply coincidental, the arithmetic errors notwithstanding. There are other examples of these kinds of data errors throughout Dr. Saed’s work, several of which were covered at his second deposition.<sup>102</sup>

5) I have also reviewed multiple drafts of Dr. Saed’s manuscript, including the version of it that was rejected by *Gynecologic Oncology* and the version later accepted by *Reproductive Sciences*. Of particular interest is the fact that the earlier submission to *Gynecologic Oncology* claimed to have observed effects of talc after only 48 hours of treatment – a fact directly addressed by one of the reviewers in the rejection letter, who wrote that the “fact that SNPs were changed following such short exposure to talcum is surprising and makes one wonder what the biological effect of such changes might be.”<sup>103</sup> Curiously, Dr. Saed’s subsequent submission to *Reproductive Sciences* changed the stated time of treatment to 72 hours – but includes many of the same tables that were included in the submission to *Gynecologic Oncology*, with exactly the same data for each dose of treatment, but with the exposure period changed from 48 hours to 72 hours. And Dr. Saed’s report states that he treated talc “for 48 hours”<sup>104</sup> – a discrepancy from his latest manuscript that he attempted to explain as “a typo” in his report at his deposition.<sup>105</sup> Of course, another possibility is that Dr. Saed decided that 72 hours of treatment would appear more credible and that he simply revised this reference in his manuscript without rerunning the experiments before he resubmitted but forgot to make the same change to his report.

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<sup>98</sup> Preliminary Work Notebook Files at 19.

<sup>99</sup> Saed Dep. Vol. I, Ex. 1 at SAED000033(color).

<sup>100</sup> *Id.*

<sup>101</sup> *Id.* at SAED000090(color).

<sup>102</sup> *See, e.g.*, Saed Dep. Vol. II 450:24-452:6, 452:22-453:24 (additional averaging errors).

<sup>103</sup> Gynecologic Oncology Decision at 2.

<sup>104</sup> Saed Rep. at 14.

<sup>105</sup> Saed Dep. Vol. I 185:6-186:7.



## E. Additional Concern

**Improper financial disclosure:** Dr. Saed's insufficient conflict-of-interest disclosure violates publishing principles and further indicates that his opinions are not reliable. Although there is no single definitive standard for an appropriate conflict-of-interest disclosure, failures to disclose conflicts of interest have undermined the faith of both the public and healthcare professionals in the quality of scientific and medical literature.<sup>106</sup> As such, most reputable journals have developed their own conflict-of-interest disclosure policies, and various voluntary organizations have advanced model standards that function as persuasive guidelines. Dr. Saed's minimal disclosure violates both these model policies and the policy in place at *Reproductive Sciences*,<sup>107</sup> the journal in which his manuscript is to be published.

For example, the International Committee of Medical Journal Editors states that authors should disclose "all financial or personal relationships that might bias or be seen to bias their work" and, in particular, notes "[f]inancial relationships (such as . . . paid expert testimony)" as the most obvious type of conflict of interest.<sup>108</sup> The World Association of Medical Editors has set forth a similar policy.<sup>109</sup> In keeping with these principles, *Reproductive Sciences* requires all authors to make a "specific" declaration of "any financial relationship" that the author has and the "interests" of the sponsoring organization, and to include any information "that might represent an appearance of a conflict of interest" in the cover letter.<sup>110</sup> Dr. Saed admits that he did not include any such information in his cover letter.<sup>111</sup> Dr. Saed did acknowledge elsewhere that he "acted as a consultant regarding this topic for a fee."<sup>112</sup> He did not link his consultancy to his manuscript in any way, much less disclose that plaintiffs' counsel funded the specific study that he submitted. Nor did he disclose that he functioned as more than a consultant, but as a testifying expert witness. Indeed, he did not even disclose for whom he consulted – whether it was a party, such as plaintiffs' counsel, with an interest in showing talc to be dangerous, a party, such as an industry player, with an interest in showing talc to be safe, or an unbiased organization. Therefore, reviewers, and ultimately readers, could not evaluate his conclusions with appropriate context in mind.

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<sup>106</sup> Blum JA et al., *Requirements and definitions in conflict of interest policies of medical journals*. JAMA. (2009) 302(20):2230-4.

<sup>107</sup> See Saed Dep. Vol. I, Ex. 12 at 3 (Sage Publishing Reproductive Sciences Webpage); see also Sage Publications, Declaration of Conflicting Interests Policy (2019), <https://us.sagepub.com/en-us/nam/declaration-of-conflicting-interests-policy>.

<sup>108</sup> Int'l Committee Med. J. Editors, *Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals* 3, <http://www.icmje.org/icmje-recommendations.pdf> (updated Dec. 2018).

<sup>109</sup> See World Ass'n of Med. Editors, *Conflict of Interest in Peer-Reviewed Medical Journals*, <http://wame.org/conflict-of-interest-in-peer-reviewed-medical-journals> (updated July 25, 2009).

<sup>110</sup> See Saed Dep. Vol. I, Ex. 12 at 3; see also Sage Publications, Declaration of Conflicting Interests Policy.

<sup>111</sup> Saed Dep. Vol. I 156:10-19.

<sup>112</sup> *Id.* 144:2-7; see also *id.* 142:1-2.

## V. MATERIALS CONSIDERED

1. A2780 Cell Line human,  
[https://www.sigmaaldrich.com/catalog/product/sigma/cb\\_93112519?lang=en&region=US](https://www.sigmaaldrich.com/catalog/product/sigma/cb_93112519?lang=en&region=US)
2. Belotte J et al., *A single nucleotide polymorphism in catalase is strongly associated with ovarian cancer survival*. PLoS One. (2015) 24;10(8):e0135739
3. Blum JA et al., *Requirements and definitions in conflict of interest policies of medical journals*. JAMA. (2009) 302(20):2230-4
4. Chu H et al., *The MPO –463G>A polymorphism and cancer risk: a meta-analysis based on 43 case–control studies*. Mutagenesis. (2010) 25(4):389-95
5. Deposition of Ghassan Saed, Ph.D., Vol. I, Jan. 23, 2019 (MDL No. 2738)
6. Deposition of Ghassan Saed, Ph.D., Vol. II, Feb. 14, 2019 (MDL No. 2738)
7. Didžiapetrienė J et al., *Significance of blood serum catalase activity and malondialdehyde level for survival prognosis of ovarian cancer patients*. Medicina (Kaunas) (2014) 50(4):204-8
8. Endo-Capron S et al., *In vitro response of rat pleural mesothelial cells to talc samples in genotoxicity assays (sister chromatid exchanges and DNA repair)*. Toxicol In Vitro. (1993) 7(1):7-14
9. Expert Report of Daniel L. Clarke-Pearson, M.D. Nov. 16, 2018 (MDL No. 2738)
10. Expert Report of Ghassan Saed, M.D., Nov. 16, 2018 (MDL No. 2738)
11. Expert Report of Judith Wolf, M.D. Nov. 16, 2018 (MDL No. 2738)
12. Expert Report of Sarah Kane, M.D., Nov. 15, 2018 (MDL No. 2738)
13. Expert Report of Shawn Levy, Ph.D., Nov. 16, 2018 (MDL No. 2738)
14. Fletcher NM et al., LB-044 – Talcum Powder Enhances Cancer Antigen 125 Levels in Ovarian Cancer Cells and in Normal Ovarian Epithelial Cells (abstract) (2018) (Ex. 21 to Deposition of Ghassan Saed, Ph.D., Jan. 23, 2019 (MDL No. 2738))
15. Fletcher NM et al., Molecular basis supporting the association of talcum powder use with increased risk of ovarian cancer (2019) (unpublished manuscript) (Ex. 8 to Deposition of Ghassan Saed, Ph.D., Jan. 23, 2019 (MDL No. 2738))
16. Fletcher NM et al., *Specific point mutations in key redox enzymes are associated with chemoresistance in epithelial ovarian cancer*. Free Radic Biol Med. (2016) 102:122-32
17. Fletcher NM et al., Talcum Powder Enhances Oxidative Stress in Ovarian Cancer, Reproductive Sciences, Vol. 25, Suppl. 1, F-098 (abstract) (2018) (Ex. 20 to Deposition of Ghassan Saed, Ph.D., Jan. 23, 2019 (MDL No. 2738))
18. Forsberg L et al., *A common functional C-T substitution polymorphism in the promoter region of the human catalase gene influences transcription factor binding, reporter gene*

- transcription and is correlated to blood catalase levels.* Free Radic Biol Med. (2001) 30(5):500-5
19. Ghassan Saed's PCR EOC SRI Notebook (Ex. 9 to Deposition of Ghassan Saed, Ph.D., Jan. 23, 2019 (MDL No. 2738))
  20. Ghassan Saed's Talc Study Lab Notebook – Preliminary Study (Ex. 23 to Deposition of Ghassan Saed, Ph.D., Feb. 14, 2019 (MDL No. 2738))
  21. Gynecologic Oncology Email dated Sept. 19, 2018 re: GYN-18-1020: Final Decision (Ex. 35 to Deposition of Ghassan Saed, Ph.D., Feb. 14, 2019 (MDL No. 2738))
  22. Hall MD et al., *Say No to DMSO: Dimethyl sulfoxide inactivates cisplatin, carboplatin and other platinum complexes.* Cancer Res. (2014) 74(14):3913-22
  23. Hamilton TC et al., *Effects of talc on the rat ovary.* Br J Exp Pathol. (1984) 65(1):101-6
  24. Harper & Saed, Talc Induces a Pro-Oxidant State in Normal and Ovarian Cancer Cells Through Gene Point Mutations in Key Redox Enzymes (Ex. 19 to Deposition of Ghassan Saed, Ph.D., Jan. 23, 2019 (MDL No. 2738))
  25. Heller DS et al., *The relationship between perineal cosmetic talc usage and ovarian talc particle burden.* Am J Obstet Gynecol. (1996) 174(5):1507-10
  26. Henderson WJ et al., *Talc and carcinoma of the ovary and cervix.* J Obstet Gynaecol Br Commonw. (1971) 78(3):266-72
  27. Int'l Agency for Research on Cancer, *Monographs on the Evaluation of Carcinogenic Risks to Humans* Vol. 93: Carbon Black, Titanium Dioxide, and Talc (2010)
  28. Int'l Committee Med. J. Editors, *Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals*, <http://www.icmje.org/icmje-recommendations.pdf> (updated Dec. 2018)
  29. Jacobs I et al., *Ovarian cancer screening and mortality in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomized controlled trial.* Lancet (2016) 387:945-56
  30. Keskin N et al., *Does long-term talc exposure have a carcinogenic effect on the female genital system of rats? An experimental pilot study.* Arch Gynecol Obstet. (2009) 280(6):925-31
  31. Klaunig JE et al., *Oxidative stress and oxidative damage in chemical carcinogenesis.* Toxicol Appl Pharmacol (2011) 25:86-99
  32. Kuchenbaecker KB et al., *Identification of six new susceptibility loci for invasive epithelial ovarian cancer.* Nat Genet. (2015) 47(2):164-71
  33. Kuchenbaecker KB et al., *Risks of breast, ovarian, and contralateral breast cancer for BRCA1 and BRCA2 mutation carriers.* JAMA (2017) 317(23):2402-16
  34. Lab Notebook, SAED000001(color)-SAED000097(color) (Ex. 1 to Deposition of Ghassan Saed, Ph.D., Jan. 23, 2019 (MDL No. 2738))

35. Malmberg K et al., *Serous tubal intraepithelial carcinoma, chronic fallopian tube injury, and serous carcinoma development*. Virchows Arch. (2016) 468(6):707-13
36. Ni X et al., *Meta-analysis on the association between non-steroidal anti-inflammatory drug use and ovarian cancer*. Br J Clin Pharmacol. (2013) 75(1):26-35
37. Norquist BM et al., *Inherited mutations in women with ovarian carcinoma*. JAMA Oncol. (2016) 2(4):482-90
38. Pharoah PD et al., *GWAS meta-analysis and replication identifies three new susceptibility loci for ovarian cancer*. Nat Genet. (2013) 45(4):362-70
39. Quick SK et al., *Effect modification by catalase genotype suggests a role for oxidative stress in the association of hormone replacement therapy with postmenopausal breast cancer risk*. Cancer Epidemiol Biomarkers Prev. (2008) 17(5):1082-7
40. Rasmussen et al., *Pelvic inflammatory disease and the risk of ovarian cancer and borderline ovarian tumors: A pooled analysis of 13 case-control studies*. Am J Epidemiol. (2017) 185(1):8–20
41. Sage Publications, Declaration of Conflicting Interests Policy (2019), <https://us.sagepub.com/en-us/nam/declaration-of-conflicting-interests-policy>
42. Sage Publications, Reproductive Sciences (Ex. 12 to Deposition of Ghassan Saed, Ph.D., Jan. 23, 2019 (MDL No. 2738))
43. Scholler N & Urban N, *CA125 in ovarian cancer*. Biomark Med (2007) 1(4):513-23
44. SK-OV-3 [SKOV-3; SKOV3] (ATCC® HTB-77™), <https://www.atcc.org/products/all/HTB-77.aspx>
45. The Role of Talc Powder Exposure in Ovarian Cancer: A Mechanistic Approach (Ex. 43 to Deposition of Ghassan Saed, Ph.D., Feb. 14, 2019 (MDL No. 2738))
46. Tomasetti C & Vogelstein B, *Variation in cancer risk among tissues can be explained by the number of stem cell divisions*. Science (2015) 347:78-81, 2015
47. TOV-112D (ATCC® CRL-11731™), <https://www.atcc.org/products/all/CRL-11731.aspx>
48. Walsh T et al., *Mutations in 12 genes for inherited ovarian, fallopian tube, and peritoneal carcinoma identified by massively parallel sequencing*. Proc Natl Acad Sci USA (2011) 108(44):18032-7
49. World Ass'n of Med. Editors, *Conflict of Interest in Peer-Reviewed Medical Journals*, <http://wame.org/conflict-of-interest-in-peer-reviewed-medical-journals> (updated July 25, 2009)
50. Zhou et al., *Pelvic inflammatory disease and the risk of ovarian cancer: a meta-analysis*. Cancer Causes Control. (2017) 28(5):415-28

# EXHIBIT A



Curriculum Vitae (02/04/19)

Name: Jeff Boyd

Place of Birth: Chapel Hill, NC

Nationality: USA

Office Address: Herbert Wertheim College of Medicine  
Florida International University  
11200 SW 8<sup>th</sup> Street, AHC2-693  
Miami, FL 33199  
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Miami Cancer Institute  
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Tel: 786-527-8023  
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Home Address: 505 Luenga Avenue  
Coral Gables, FL 33146

Education: Duke University, Durham, NC  
B.S. (Psychology/Chemistry), 1980

NC State University, Raleigh, NC  
M.S. (Toxicology/Biochemistry), 1982

NC State University, Raleigh, NC  
Ph.D. (Toxicology/Biochemistry), 1986

Postdoctoral Training: 1986-1988: Environmental Pathology Fellowship  
Department of Pathology  
Lineberger Comprehensive Cancer Center  
University of North Carolina School of Medicine  
Chapel Hill, NC

1988-1990: Senior Staff Fellow  
Cellular Carcinogenesis Section  
Laboratory of Molecular Carcinogenesis  
NIH/National Institute of Environmental Health Sciences  
Research Triangle Park, NC

Positions and Appointments:

1990-1994: Head, Gynecologic Pathobiology Section  
Laboratory of Molecular Carcinogenesis  
NIH/National Institute of Environmental Health Sciences  
Research Triangle Park, NC

1992-1994: Adjunct Assistant Professor (concurrent with primary position above)  
Department of Epidemiology  
University of North Carolina School of Public Health  
Chapel Hill, NC

1994-1997: Associate Professor  
Department of Obstetrics and Gynecology and Department of Genetics  
Director, Gynecologic Oncology Research Laboratory  
Member, Comprehensive Cancer Center  
Member, Center for Research on Women's Health and Reproduction  
Associate Member, Institute for Human Gene Therapy  
University of Pennsylvania  
Philadelphia, PA

1997-2003: Associate Attending Biologist  
Gynecology Service, Department of Surgery  
Clinical Genetics Service, Department of Medicine  
Director, Gynecology and Breast Research Laboratory  
Memorial Hospital for Cancer and Allied Diseases  
Associate Member, Memorial Sloan-Kettering Cancer Center  
New York, NY

2003-2006: Attending Biologist  
Gynecology Service, Department of Surgery  
Clinical Genetics Service, Department of Medicine  
Director, Gynecology and Breast Research Laboratory (Department of Surgery)  
Director, Diagnostic Molecular Genetics Laboratory (Department of Medicine)  
Memorial Hospital for Cancer and Allied Diseases  
Member (with tenure-of-title), Memorial Sloan-Kettering Cancer Center  
New York, NY

2006-2007: Vice President, Laboratory Science  
2007-2008: Vice President, Oncology and Research  
2007-2008: Director, Curtis and Elizabeth Anderson Cancer Institute  
2006-2008: Professor of Obstetrics and Gynecology, Surgery, Medicine, and Division of  
Basic Medical Sciences, Mercer University School of Medicine - Savannah  
Assistant Dean for Research, Mercer University School of Medicine - Savannah  
Distinguished Cancer Scholar, State of Georgia  
Memorial University Medical Center, Savannah, GA

2008-2010: Senior Vice President and Chief Scientific Officer  
Robert C. Young, MD, Chair in Cancer Research  
Professor (with tenure), Women's Cancer Program  
Fox Chase Cancer Center, Philadelphia, PA

2010-2014: Senior Vice President, Molecular Medicine  
Robert C. Young, MD, Chair in Cancer Research  
Executive Director, Cancer Genome Institute  
Chief, Division of Molecular Pathology  
Professor (with tenure), Cancer Biology Program  
Fox Chase Cancer Center, Philadelphia, PA

2008-2015: Professor (with tenure), Cancer Biology Program  
Robert C. Young, MD, Chair in Cancer Research  
Fox Chase Cancer Center, Philadelphia, PA

2015-present: Professor (with tenure) and Chair, Department of Human and Molecular  
Genetics  
Professor, Department of Obstetrics and Gynecology  
Associate Dean for Basic Research and Graduate Programs  
Herbert Wertheim College of Medicine  
Florida International University  
Miami, FL

2015-present: Associate Deputy Director, Translational Research and Genomic Medicine  
Miami Cancer Institute  
Baptist Health South Florida  
Miami, FL

Scientific and Medical Societies:

American Association for the Advancement of Science (1982)  
American Association for Cancer Research (1990)  
American Society for Cell Biology (1992)  
American Society of Clinical Oncology (2002)  
American Society of Human Genetics (1997)  
Association for Molecular Pathology (2014)  
International Society of Gynecologic Oncology (2006)  
Society of Gynecologic Oncology (1997)

Awards, Fellowships, and Grants:

Award for Special Achievement  
Department of Health, Education, and Welfare, NIH, July, 1980.

Environmental Pathology Training Fellowship (Institutional NRSA)  
NIH/NIEHS, T32-ES07017, March, 1986.

National Research Service Award (Individual)  
NIH/NCI, F32-CA0524, February, 1988.

Co-Principal Investigator, Gynecologic Cancer Foundation/Karin Smith Award,  
“Gene Therapy of Ovarian Cancer” (Univ of Pennsylvania); 6/1/96-5/31/97;  
\$50,000 total direct costs.

Principal Investigator, “Molecular Genetics of Gynecologic Cancers”  
NIH/NCI, R01-CA67164; 10/1/96-9/30/00; \$482,401 total direct costs.

Principal Investigator, “Genetic Mechanism of BRCA1-Linked Ovarian Tumorigenesis”,  
NIH/NCI, R01-CA71840, 10/1/96-9/30/00; \$465,563 total direct costs.

Principal Investigator, “Genetic Mechanism of BRCA-Linked Ovarian Tumorigenesis”,  
NIH/NCI, R01-CA71840, 2/1/01-1/31/05; \$676,000 total direct costs.

Principal Investigator, “Basic and Translational Research Program in the Molecular  
Genetics of Gynecologic and Breast Cancers: New Strategies for Prevention, Early  
Detection, and Treatment”, Keck Foundation; 1/1/99-12/31/03; \$2,500,000 direct costs.

Principal Investigator, “Molecular Classification of Ovarian Cancers”,  
NIH/NCI, U01-CA88175; 10/1/00-9/30/05; \$655,976 total direct costs.

Principal Investigator, “Preclinical Alterations in Breast Epithelium of BRCA Heterozygotes”, Breast Cancer Research Foundation, 10/1/00; \$170,000 total direct costs.

Principal Investigator, “Molecular Genetic Basis of Invasive Breast Cancer Risk Associated with Lobular Carcinoma in Situ”, Breast Cancer Research Foundation, 10/1/01; \$243,356 total direct costs.

Principal Investigator, “Prediction of Breast Cancer Risk by Gene Expression Profiling”, Breast Cancer Alliance, 11/1/01; \$130,000 total direct costs.

Principal Investigator, “Molecular Response to Selective Estrogen Receptor Modulators (SERMs) in Human Breast Cancer Cells”, Breast Cancer Research Foundation, 10/1/02; \$228,862 total direct costs.

Principal Investigator, “Genetic Polymorphisms and Risk of Breast Cancer”, Breast Cancer Alliance, 11/1/02; \$91,592 total direct costs.

Principal Investigator, “Somatic Genetic Alterations in *BRCA*-Linked Human Breast Cancer”, Breast Cancer Research Foundation, 10/1/03; \$230,000 total direct costs.

Principal Investigator, “Molecular Classification of Endometrial Cancers”, NIH/NCI, R01-CA100272; 4/1/04-3/31/08; \$1,350,000 total direct costs.

Principal Investigator, “Prediction of Breast Cancer Risk by Whole Genome Profiling”, Department of Defense, CDMRP, BC033728; 8/1/04-7/31/05; \$75,000 total direct costs.

Principal Investigator, “Prediction of Breast Cancer Risk by Whole Genome Profiling”, Breast Cancer Research Foundation, 10/1/04; \$250,000 total direct costs.

Project Director, “Project 1: Role of CA125/MUC16 in Ovarian Tumorigenesis”, NIH/NCI, P01-CA52477-13, “Epithelial Ovarian Cancer Program Project”; 4/1/05-3/31/10; \$7,374,628 total direct costs.

Co-Principal Investigator, “Polygenic Basis of Breast Cancer”, Breast Cancer Research Foundation, 10/1/05; \$250,000 total direct costs.

Georgia Distinguished Cancer Scholar, Georgia Cancer Coalition, 2006-2010; \$750,000 total direct costs.

Principal Investigator, “Recruiting shRNA Functional Screening Expertise”, Pennsylvania Department of Community and Economic Development Grant, C000043689, 1/1/09-6/30/10; \$150,000 total costs.



Principal Investigator, American Cancer Society Institutional Research Grant, IRG-92-027-15, 1/1/08-12/31/10; \$360,000 total costs.

Principal Investigator, “The Exomes of Ovarian Tumors of Low Malignant Potential and Low Grade Ovarian Cancers”, Sandy Rollman Ovarian Cancer Foundation; 6/1/10-5/31/11; \$60,000 direct costs.

Mentor, “Determine the Role of Canonical Wnt Signaling in Ovarian Tumorigenesis”, CDMRP/DOD, Ovarian Academy Award W81XWH-10-1-0823 (PI: R Zhang), 9/15/10-3/29/13; \$750,000 total direct costs.

Angela Carlino Excellence in Ovarian Cancer Research Award, Sandy Rollman Ovarian Cancer Foundation; October, 2010.

Principal Investigator, “The Transcriptome of Platinum Resistance in Ovarian Cancer”, The Carpenter Foundation; 7/1/12-6/30/13; \$50,000 total direct costs.

Principal Investigator, “FCCC-PENN SPORE in Ovarian Cancer”, NIH/NCI, P50 CA083638; 8/21/09–5/31/15; \$9,996,150 total direct costs.

Mentor, “Identifying Determinants of PARP Inhibitor Sensitivity in Ovarian Cancer”, CDMRP/DOD, Ovarian Academy Award OC130212 (PI: N Johnson), 2/1/14-1/31/19; \$750,000 total direct costs.

Rosalind Franklin Award for Excellence in Ovarian Cancer Research, Ovarian Cancer Research Fund Alliance; July, 2016.

Co-Investigator, “The Impact of Radiation Dose on Brain Morphology, Volumetric Changes, Endocrine Function, and Neurocognitive Function Following Cranial Radiation Therapy in Children with Brain and Skull Base Tumors”, Florida Department of Health, Award 8LA04 (PI: M. Hall), 6/14/18-4/30/22; \$700,000 total direct costs.

#### Editorial Positions:

1993-1997:	Associate Editor, <i>Molecular and Cellular Differentiation</i>
1994-2006:	Associate Editor, <i>Molecular Carcinogenesis</i>
1997-2003:	Editorial Board, <i>Gynecologic Oncology</i>
2003-2008:	Associate Editor, <i>Gynecologic Oncology</i>
2004-2008:	Editorial Board, <i>Journal of Clinical Oncology</i>
2004-2017:	Editorial Board, <i>American Journal of Pathology</i>
2017-present	Editorial Board, <i>Anticancer Research</i>

Committee Assignments (Previous):

Member, Task Force for Activities and Membership Development,  
American Association for Cancer Research, 1993.

Member, Epidemiology Committee, DOD Breast Cancer Program Review, 1994.

Member, Program Committee, Annual Meeting of the American Association for Cancer  
Research, 1995.

Member, Physiology Committee, DOD Gulf War Illness Program Review, 1995.

Member, Reproductive Biology Committee, DOD Women's Health Program Review,  
1996.

Member, Special Review Group, "Endocrine Disrupting Chemicals and Women's Health  
Outcomes" (RFA 96-003), NIH/NIEHS, 1996.

Member, Epidemiology Committee, DOD Breast Cancer Program Review, 1996.

Invited Participant, American Cancer Society Workshop on Heritable Cancer Syndrome  
and Genetic Testing, 1996.

Member, Special Review Panel for Program Project Application P01-CA73992,  
"Molecular and Clinical Approaches to Colon Cancer Precursors", University of Utah,  
1996.

Ad-Hoc Member, Program Committee, Society for Gynecologic Oncologists Annual  
Meeting, 1997.

Invited participant, "The Strategic Planning Conference on New Directions in Ovarian  
Cancer Research", The U.S. Public Health Service's Office on Women's Health,  
Washington, DC, 1997.

Member, Committee for DOD Ovarian Cancer Program Review, 1998.

Invited participant, "Implementation Meeting for New Directions in Ovarian Cancer  
Research", The National Cancer Institute and The Society of Gynecologic Oncologists,  
Bethesda, MD, 1998.

Member, Special Review Panel for National Cancer Institute Program Project Grant  
Application, "Epidemiologic and Genetic Studies of Breast Cancer", Mayo Foundation,  
Rochester, MN, February, 1999.

Ad Hoc Member, National Cancer Institute Scientific Review Group, Subcommittee E (Prevention and Control), Bethesda, MD, 1999.

Ad-Hoc Member, Initial Review Group, Small Grants Program for Cancer Epidemiology, National Cancer Institute, Bethesda, MD, 1999.

Ad-Hoc Member, Peer Review Committee on Molecular Genetics and Oncogenes, American Cancer Society, 1999.

Member, Specified Appropriations Program Peer Review Committee, United States Army Medical Research and Material Command, 1999.

Member, Committee for DOD Ovarian Cancer Program Review, 1999.

Member, Special Review Panel for National Cancer Institute Program Project Grant Application, "DNA Repair Genes and Cancer", University of Kentucky Medical Center, Lexington, KY, September, 1999.

Member, Program Committee, Society of Gynecologic Oncologists Annual Meeting, 2000.

Member, Special Review Panel for National Cancer Institute Program Project Grant Application, "Dietary and Hormonal Determinants of Cancer in Women" (Nurses' Health Study), Brigham and Women's Hospital, Boston, MA, February, 2000.

Invited Participant, Gynecologic Cancer Translational Research Retreat (GOG/NCI), Chantilly, VA; May, 2000.

Course Director, Second International Conference on Ovarian Cancer, Memorial Sloan-Kettering Cancer Center, New York, NY; June, 2000.

Invited Participant, Conference on Ovarian Cancer Screening, NCI, Bethesda, MD; September, 2000.

Member, Committee for DOD Ovarian Cancer Program Review, 2000.

Invited Participant, NCI Gynecologic Cancers Progress Review Group Roundtable Meeting, Herndon, VA; June, 2001.

Member, Committee for DOD Ovarian Cancer Program Review, 2001.

Ad-Hoc Member, PTHC/CAMP Scientific Review Group, National Institutes of Health, Washington, DC; June, 2002.

Member, Epidemiology Panel, DOD Breast Cancer Program Review, 2002.

Member, Special Review Panel for National Cancer Institute Program Project Grant Application, “Cervical Cancer: Biology of Initiation and Progression”, Emory University, Atlanta, GA, September, 2002.

Member, Scientific Review Group for Ovarian SPORE Applications, National Cancer Institute, Bethesda, MD; June, 2003.

Invited participant, Borderline Ovarian Tumor Consensus Workshop, National Cancer Institute, Bethesda, MD; August, 2003.

Member, Special Emphasis Panel ZCA1 SRRB-4 J1 R, “Strategic Partnerships to Evaluate Cancer Signatures”, National Institutes of Health, 2004.

Member, Program Committee, Society of Gynecologic Oncologists Annual Meeting, Miami Beach, FL; 2005.

Ad-Hoc Member, NCI Scientific Review Group, Subcommittee E – Cancer Epidemiology, Prevention, and Control, Bethesda, MD; April, 2005.

Chair, Special Emphasis Panel, ZRG1 ONC-U (03), Breast and Ovarian Cancer Genetics, Center for Scientific Review, National Institutes of Health; July, 2005.

Invited Participant, National Cancer Institute Ovarian Cancer State-of-the-Science Meeting, Bethesda, MD; September, 2005.

Member, Education Committee, Society of Gynecologic Oncologists, 2000-2004  
Member, Institutional Review Board, Memorial Sloan-Kettering Cancer Center, 1999-2006.

Member, Human Tissue Utilization Committee, Memorial Sloan-Kettering Cancer Center, 2002-2006.

Member, Computational Biology Program Search Committee, Memorial Sloan-Kettering Cancer Center, 2002-2006.

Member, Database Working Group, Memorial Sloan-Kettering Cancer Center, 2002-2006.

Ad-Hoc Member, Committee on Appointments and Promotions, Memorial Sloan-Kettering Cancer Center; July 2002, October, 2003, April, 2004, March, 2005.\

Member, Translational and Integrative Medicine Grant Review Committee, Memorial Sloan-Kettering Cancer Center; 2003-2006.

Member, Institutional Review Board Workflow Committee, Memorial Sloan-Kettering Cancer Center; 2004-2006.

Invited Participant, Joint NCI/British National Cancer Research Institute Gynecologic Cancer Intergroup Endometrial Cancer State-of-the-Science Meeting, Manchester, UK; November, 2006.

Member, Integration Panel, DOD Ovarian Cancer Research Program, 2001-2008.

Chair, Integration Panel, DOD Ovarian Cancer Research Program, 2005-2006.

Member, Peer Review Committee on Molecular Genetics and Oncogenes, American Cancer Society, 2002-2006.

Charter Member, Cancer Biomarkers Study Section, Center for Scientific Review, National Institutes of Health, 2003-2008.

Chair, Molecular and Cellular Biology and Genetics Peer Review Panel, Susan G. Komen for the Cure Grants Program; January, 2008.

Member, External Advisory Committee, SPORE in Ovarian Cancer, Fox Chase Cancer Center, Philadelphia, PA; 2003-2008.

Chair, Appointments and Promotions Committee, Anderson Cancer Institute, Memorial University Medical Center; 2006-2008.

Member, Board of Directors, Georgia Center for Oncology Research and Education; 2006-2008.

Member, Georgia Cancer Coalition Distinguished Cancer Scholar Review Committee; 2006-2008.

Chair, Medical Research Advisory Committee, Memorial University Medical Center; 2007-2008.

Member, Board of Advisors, College of Science and Technology, Georgia Southern University; 2006-2008.

Member, Special Emphasis Panel, NCI-ARRA P30 Biomedical Research Core Center Review, Rockville, MD; July, 2009.

Member, CDMRP Ovarian Cancer Grant Review Panel OC-4, Reston, VA; August, 2009.



Member, Scientific Advisory Committee, Ovarian Cancer Research Fund, 1999-2009.

Chair, DOD/CDMRP Breast Cancer Grant Review Panel MBG-B, Reston, VA; January, 2010.

Member, Scientific Review Group, NIH/NCI ZCA1 SRLB-R M1 R, Exceptional, Unconventional Research Enabling Knowledge Acceleration (EUREKA), Rockville, MD; March, 2010.

Member, Scientific Review Group, EDRN Biomarker Development Labs (U01), NIH/NCI ZCA1 SRLB-C M1 B, Bethesda, MD; May, 2010.

Chair, DOD/CDMRP Breast Cancer Research Program Grant Review Panel TRN-MBG, Reston, VA; May, 2010.

Chair, DOD/CDMRP Breast Cancer Research Program Grant Review Panel IDEA-MBG, Reston, VA; June, 2010.

Chairman, External Advisory Committee, SPORE in Ovarian Cancer, Dana-Farber/Harvard Cancer Center, Boston, MA; 2003-2010.

Member, Program Committee, 13<sup>th</sup> Biennial Meeting of the International Gynecologic Cancer Society, Prague, Czech Republic, 2010.

Member, Nominations Committee, Fox Chase Cancer Center, 2008-2010.

Member, Scientific Review Group, NIH/NCI ZCA1 SRLB-2 M1 R, Exceptional Unconventional Research Enabling Knowledge Acceleration (EUREKA), Bethesda, MD; March, 2011.

Member and Co-Chair, Subcommittee on Tissue Utilization, Gynecologic Oncology Group, 1997-2011.

Member, Scientific Review Group, NIH/NINR ZNR1 REV M 09, Personalized Genomics for Symptom Management: Bridging the Gaps from Genomic Discovery to Improved Health Outcomes, Bethesda, MD; June, 2011.

Member, Program Committee, Society for Gynecologic Oncology Annual Meeting, 2012.

Member, Board of Directors, Gynecologic Cancer Foundation (now Foundation for Women's Cancer); 2006-2013.

Member, Cancer Center Support Grant Executive Committee, Fox Chase Cancer Center, 2008-2013.

Member, President's Council, Fox Chase Cancer Center, 2008-2013.

Chair, DOD/CDMRP Breast Cancer Research Program Grant Review Panel BC12 TRN2, Reston, VA; February, 2013.

Member, Scientific Review Group, NCI ZCA1 RPRB-O (O1), NCI Small Grants Program for Cancer Research (NCI Omnibus R03), Reston, VA; June, 2013.

Member, Scientific Review Committee, DOD/CDMRP Ovarian Cancer Research Program Pilot Award Letter of Intent Review; July, 2013.

Chair, DOD/CDMRP Breast Cancer Research Program Grant Review Panel TRN2-CMB, Chantilly, VA; March, 2014.

Member, Executive Committee on Research, Fox Chase Cancer Center, 2008-2014.

Member, Scientific Review Committee, DOD/CDMRP Ovarian Cancer Research Program Pilot Award Letter of Intent Review; July, 2014.

Member, NCI Special Emphasis Panel for Review of Omnibus R21/R03 Applications in Response to PAR12-145/144; July, 2014.

Member, Scientific Review Committee, DOD/CDMRP Breast Cancer Research Program Grant Review Panel CBY-2, Reston, VA; July, 2014.

Member, Ovarian Cancer SPORE Executive Committee, Fox Chase Cancer Center, 2008-2015.

Founding Member, Genomic Advisory (Tumor) Board, Fox Chase Cancer Center, 2012-2015.

Member, Program Committee, Society of Gynecologic Oncology Annual Meeting, Chicago, IL; March, 2015.

Member, DOD/CDMRP Ovarian Cancer Research Program Pre-Application Review Panel, Pilot Award Mechanism; May-June, 2015.

Chair, DOD/CDMRP Breast Cancer Research Program Grant Review Panel, Molecular Biology and Genetics, Reston, VA; June, 2015.

Chair, Society of Gynecologic Oncology Genetics Delivery Care Summit, 2014-2015.

Invited Participant, Workshop on Ovarian Cancer, US Food and Drug Administration, White Oak, MD; July, 2015.

Member, Novartis Future of Diagnostic Laboratories Advisory Board, Austin, TX; November, 2015.

Invited Participant, Banbury Center Conference on, “Preventing BRCA-Related Cancer: a Think Tank for Innovative Strategies, Milestone Objectives, and Research Priorities”, Cold Spring Harbor, NY; November, 2015.

Member, Committee on Experimental Medicine, Gynecologic Oncology Group (now NRG Oncology), 1997-2014.

Co-Chair, Banbury Center Conference on, “After UKCTOCS: Public Messaging on Screening and Early Detection of Ovarian Cancer”, Cold Spring Harbor, NY; February, 2016.

Member, FORCE (Facing Our Risk of Cancer Empowered) Advisory Board; 2003-2013.

Member, Development Committee, Foundation for Women’s Cancer, 2013-2015.

Member, National Cancer Institute Special Emphasis Panel/Scientific Review Group 2016/05 ZCA1 PCRB-C (C2) B - Cell and Animal Models for Researching Disparities; February, 2016.

Chair, DOD/CDMRP Ovarian Cancer Research Program Grant Review Panel, Pathobiology Pilot Award Program; September, 2016.

Member, Clinical Practice Committee, Society of Gynecologic Oncology, 2014-2017.

Member, AACR Clinical and Translational Cancer Research Grants Scientific Review Committee, 2015-2017.

Member, National Cancer Institute Clinical Translational R21 and Omnibus R03 Special Emphasis Panel ZCA1 SRB-P (O1); May, 2018.

Member, Medical Student Interview Panel, Herbert Wertheim College of Medicine, Florida International University; 2017-2018.

Member, National Cancer Institute Special Emphasis Panel, ZCA1 SRB-P (J1) – Clinical and Translational Exploratory/Developmental Studies; September, 2018.

Co-Chair, Banbury Center Conference on, “Towards a Cure for Advanced Ovarian Cancer”, Cold Spring Harbor, NY; October, 2018.

Member, Scientific Advisory Committee, Ovarian Cancer Research Alliance, 2001-2018.

Chair, Scientific Advisory Committee, Ovarian Cancer Research Alliance, 2009-2018.

Member, Board of Directors, Ovarian Cancer Research Fund Alliance, 2012-2018.

Member, Scientific Review Committee, National Cancer Institute Specialized Programs of Research Excellence II (P50); 2019/05 ZCA1 RPRB-7 (M1) P; January, 2019.

Member, Special Emphasis Panel-5, National Cancer Institute Clinical and Translational R21 and Omnibus R03; 2019/05 ZCA1 SRB-P (M2) S; January, 2019.

Committee Assignments (Current):

Member, External Advisory Board, SPORE in Ovarian Cancer, MD Anderson Cancer Center, Houston, TX; 2009-present.

Vice-Chair, Joint Scientific Advisory Committee, Stand Up to Cancer (SU2C) Ovarian Cancer Dream Team Grant; 2014-present.

Member, Cancer Education Committee: Cancer Prevention, Hereditary Genetics, and Epidemiology Track, American Society of Clinical Oncology (ASCO); 2016-present.

Member, Clinical Scientific Review Committee, Miami Cancer Institute, 2016-present.

Member, Board of Directors, Society of Gynecologic Oncology, 2017-2020.

Member, Medical Student Interview Panel, Herbert Wertheim College of Medicine, Florida International University; 2018-2019.

Member, Board of Directors, Florida International University Research Foundation; 2017-present.

Invited Lectures (Since 1992):

"Cell structure and tumor suppression" and "Molecular genetic techniques in human cancer research." South American Course in Cancer Research; Caracas, Venezuela; February, 1992.

"Form and function in molecular carcinogenesis." Third Frontiers in Science Symposium; NIH/NIEHS, Research Triangle Park, NC; April, 1992.

"Expression and function of the DCC gene in neural differentiation." Gordon Research Conference on Cancer; Newport, RI; August, 1992.

"DCC gene expression and function." Fifth Conference on Differentiation Therapy; Sardinia, Italy; September, 1992.

"Tumor suppressor genes I" and "Tumor suppressor genes II." Department of Toxicology, North Carolina State University, Raleigh, NC; September, 1992.

"Molecular genetics of human endometrial carcinoma." Department of Pathology, University of North Carolina, Chapel Hill, NC; September, 1992.

"Methods for the study of molecular genetics in human cancer." Department of Pathology, Jikei University School of Medicine, Tokyo, Japan; October, 1992.

"The role of cell structure in tumor suppression." Fourth International Conference of Anticancer Research; Crete, Greece; October, 1992.

"Molecular markers and endometrial cancer." Department of Epidemiology, University of North Carolina School of Public Health, Chapel Hill, NC; November, 1992.

"Tumor suppressor genes." Department of Epidemiology, University of North Carolina, Chapel Hill, NC; November, 1992.

"Role of cell and tissue structure in tumor suppression." Department of Pathology, Johns Hopkins University School of Medicine, Baltimore, MD; November, 1992.

"Endometrial hyperplasia and adenocarcinoma: Molecular genetic characterization and determinants of risk." American Association of Pathologists Annual Meeting; New Orleans, LA; March, 1993.

"The environment and women's health." First Annual Environmental Careers Symposium; NIH/NIEHS, Research Triangle Park, NC; May, 1993.



"Cell structure and tumor suppression." Gordon Research Conference on Biological Structure and Gene Expression; Volterra, Italy; May, 1993.

"Molecular genetics of human endometrial carcinoma." Department of Molecular and Cell Biology, University of California at Berkeley, Berkeley, CA; May, 1993.

"Molecular genetics of human endometrial carcinoma." Gordon Research Conference on Hormonal Carcinogenesis; Newport, RI; August, 1993.

"Molecular genetics of endometrial hyperplasia." Workshop on Alternatives to Hysterectomy, National Institutes of Health, Bethesda, MD; May, 1994.

"Molecular genetics of ovarian carcinoma." Third International Symposium on Ovarian Function, Sapporo, Japan; September, 1994.

"Molecular genetics of estrogen-associated cancers." Conference on Molecular Mechanisms of Environmental Carcinogenesis, Research Triangle Park, NC; September, 1994.

"Molecular genetics of gynecologic cancers." University of Pennsylvania Cancer Center Symposium on New Developments in Cancer Therapy: Focus on Gynecologic Cancers, Philadelphia, PA; December, 1994.

"Genetics and molecular medicine for the gynecologic oncologist", "BRCA1 and other genes involved in hereditary predisposition to reproductive cancer", Society of Gynecologic Oncologists Annual Meeting, San Francisco, CA; February, 1995.

"Hereditary Gynecologic Cancers." Grand Rounds, Department of Obstetrics and Gynecology, University of Pennsylvania Medical Center, Philadelphia, PA; March, 1995.

"Endometriosis and the Environment: Biomarkers of Toxin Exposure." Endometriosis 2000 Conference, National Institutes of Health, Bethesda, MD; May, 1995.

"Hereditary Gynecologic Cancers." Grand Rounds, Department of Obstetrics and Gynecology, Medical College of Pennsylvania, Philadelphia, PA; May 1995.

"E-Cadherin as a Tumor Suppressor." Gordon Research Conference on Cell Contact and Adhesion, Andover, NH; June, 1995.

"Mismatch Repair." American Urologic Association Summer Research Conference, Houston, TX; August, 1995.

“Genetic Characterization of Human Endometrial Carcinoma.” Ninth International Conference on Carcinogenesis and Risk Assessment, Austin, TX; November, 1995.

“Molecular Genetics of Ovarian Carcinoma.” The Finnish Medical Society Duodecim Annual Meeting, Turku, Finland; November, 1995.

“Hereditary Gynecologic Cancers.” Department of Pathology Grand Rounds, University of Pennsylvania Medical Center, Philadelphia, PA; November, 1995.

“Genetics of Hereditary Breast and Gynecologic Cancers.” Postgraduate Course on Molecular Biology of Gynecologic Cancers: Clinical Implications for the 1990s. Society of Gynecologic Oncologists Annual Meeting, New Orleans, LA; February, 1996.

“Molecular Genetics of Hereditary Gynecologic Cancers.” Department of Obstetrics and Gynecology Grand Rounds, Thomas Jefferson University, Philadelphia, PA; February, 1996.

“Hereditary Nonpolyposis Colorectal Cancer: Ethical, Legal, and Social Implications of Genetic Testing and Counseling for High Risk Individuals.” American Radium Society Annual Meeting, San Francisco, CA; March, 1996.

“Molecular Genetics of Hereditary Gynecologic Cancers.” Department of Genetics, University of Pennsylvania, Philadelphia, PA; May, 1996.

“Molecular Genetics of Hereditary Endometrial and Ovarian Carcinomas.” President’s Symposium of the New York Pathological Society, New York, NY; June, 1996.

“Familial Ovarian Cancer: Laboratory Diagnosis.” Current Concepts in Women’s Health Care: Seventeenth Annual Postgraduate Course, University of Pennsylvania Medical Center, Philadelphia, PA; June 1996.

“Molecular Genetics of Hereditary Gynecologic Cancers.” Barbara Moore Jordan Visiting Professorship, Memorial Sloan-Kettering Cancer Center, New York, NY; July 1996.

“Breast Cancer Genetics.” Keynote Lecture at the First Annual New Jersey Breast Cancer Research Symposium, Princeton, NJ; October, 1996.

“Estrogen as a Human Carcinogen: Molecular Genetics of Gynecologic Cancers.” US-Japan Cooperative Medical Science Program, Environmental Mutagenesis and Carcinogenesis Panel, Tokyo, Japan; November, 1996.

“Hereditary Breast and Ovarian Cancer: Molecular Genetics and Clinical Implications.” Grand Rounds, Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY; December, 1996.

“Molecular Genetics of Hereditary Gynecologic Cancers.” Solid Tumor Oncology Conference, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY; February, 1997.

“Molecular Genetics of Hereditary Ovarian Cancer.” Basic Science Postgraduate Course; “BRCA1/2 and Other Genes Involved in Hereditary Predisposition to Ovarian Cancer.” Breakfast Session, Society of Gynecologic Oncologists Annual Meeting, Phoenix, AZ; March, 1997.

“Genetics of Ovarian Cancer.” Helene Harris Memorial Trust 6th International Forum on Ovarian Cancer, Los Angeles, CA; May, 1997.

“Genotype-Phenotype Correlations in Hereditary Ovarian Cancer.” Symposium on Ovarian Cancer: Prevention, Genetics and Treatment Challenges, Toronto, Ontario; May, 1997.

“Molecular Genetics of Hereditary Gynecologic Cancers.” Department of Pathology Grand Rounds, Memorial Sloan-Kettering Cancer Center, New York, NY; July, 1997. “Quantitative Methods in Cancer Genetics.”

Cancer Genetic Counseling and Testing: A Multidisciplinary Course, The Sarah Lawrence College Human Genetics Program, New York, NY; July, 1997.

“Hereditary Gynecologic Cancers: Molecular Genetics and Clinical Implications.” 26th Congress of Gynecologic Pathology and Colposcopy, Tokyo, Japan; July, 1997.

“Molecular Genetics of Estrogen-Associated Human Cancers.” Gordon Research Conference on Hormonal Carcinogenesis, Tilton, NH; July, 1997.

“Basic Principles of Genetics for Practicing Clinicians”, Genetic Techniques - Relevance for Practicing Clinicians”, and “Genetics of Gynecologic Sarcomas and Clinical Implications”. European School of Oncology Conference on Molecular Genetics in Gynecologic and Breast Cancer and Its Clinical Implications: Bridging the Gap, Budapest, Hungary; November, 1997.

“Studies on the Molecular Mechanism of Estrogen-Associated Human Cancers.” Department of Biochemistry, Mount Sinai University School of Medicine, New York, NY; November, 1997.

“Molecular Genetics of Hereditary Gynecologic and Breast Cancers.” Distinguished Lecturer in Oncology, University of Texas M.D. Anderson Cancer Center, Houston, TX; January, 1998.

“Genetics of Hereditary Gynecologic Cancers: What patients are asking their gynecologists.” Obstetrical Society of Philadelphia, Philadelphia, PA; February, 1998.

“Molecular Genetics of Hereditary Gynecologic Cancers.” Grand Rounds, Department of Obstetrics and Gynecology, Allegheny University of the Health Sciences, Philadelphia, PA; February, 1998.

“Endometrial Cancer.” Course on Human Genetics and Human Cancer, Memorial Sloan-Kettering Cancer Center, New York, NY; May, 1998.

“Molecular Genetics of Hereditary Gynecologic Cancers: Clinical Implications.” New York Gynecology Society, New York, NY; May, 1998.

“Hereditary Ovarian Cancer: Molecular Genetics and Clinical Implications.” IVth Sapporo International Symposium on Ovarian Function, Sapporo, Japan; August, 1998.

“Molecular Pathogenesis of Endometrial Neoplasia.” Grand Rounds, Department of Pathology, Brigham and Women’s Hospital, Boston, MA; October, 1998.

“Hereditary Gynecologic Cancers: Molecular Genetics and Clinical Implications.” Visiting Professor Program, Department of Pathology, Montefiore Medical Center, Bronx, NY; October, 1998.

“Molecular Genetics of Hereditary Gynecologic Cancers.” Memorial Hospital Annual Alumni Meeting, Memorial Sloan-Kettering Cancer Center, New York, NY; November, 1998.

“Clinical and Pathologic Features of BRCA-Associated Hereditary Ovarian Cancers.” Grand Rounds, Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY; November, 1998.

“Genetic Epidemiology of Ovarian Cancer.” International Conference on Ovarian Cancer, The University of Texas M.D. Anderson Cancer Center, Houston, TX; February, 1999.

“Ovarian Cancer.” Course on Human Genetics and Human Cancer, Memorial Sloan-Kettering Cancer Center, New York, NY; April, 1999.

“Genetics of Ovarian Cancer.” Annual Conference of the National Corporate Medical Associates, Memorial Sloan-Kettering Cancer Center, New York, NY; June, 1999.

"Molecular Genetics of Hereditary Gynecologic Cancers." Scientific Symposium for Semi-Annual Business meeting of the Gynecologic Oncology Group, Scottsdale, AZ; July, 1999.

"Genetics." Breast Cancer Core Course, Memorial Sloan-Kettering Cancer Center, New York, NY; July, 1999.

"Genetic Susceptibility to Gynecologic Cancers." Cancer Smart Lecture Series, Memorial Sloan-Kettering Cancer Center, New York, NY; October, 1999.

"Molecular Genetics of Hereditary Breast Cancer: Clinical Implications." New York Pathological Society, New York, NY; February, 2000.

"Genetics of Hereditary Gynecologic Cancers." Postgraduate Course at the Society of Gynecologic Oncologists Annual Meeting, San Diego, CA; February, 2000.

"Molecular Genetics of Breast and Gynecologic Cancers." Course on Molecular Oncology, New York University School of Medicine, New York, NY; March, 2000.

Session Chair, Conference on Gynecologic Care of the Cancer Patient, Memorial Sloan-Kettering Cancer Center, New York, NY; March, 2000.

"Molecular Genetic Mechanism of Estrogen-Associated Human Tumorigenesis." Memorial Sloan-Kettering Cancer Center Scientific Retreat, March, 2000.

"Biology of Ovarian Cancer." Disease Management Team Conference Series (Gynecology), Memorial Sloan-Kettering Cancer Center, New York, NY; March, 2000.

"Preclinical Molecular Genetic Alterations in Breast and Ovarian Epithelium of BRCA Heterozygotes." American College of Surgeons Oncology Group Planning Conference. Memorial Sloan-Kettering Cancer Center; April, 2000.

Session Chair, Molecular Biology of Gynecologic Cancers, American Association for Cancer Research Annual Meeting, San Francisco, CA; April, 2000.

"Genetics of Hereditary Ovarian Cancer." Education Session on Ovarian Cancer, American Society of Clinical Oncology Annual Meeting, New Orleans, LA; May, 2000.

"Genetic Analysis of Ovarian Carcinoma Histogenesis." Ovarian Cancer National Alliance Third Annual Advocacy Conference, Washington, DC; September, 2000.

"Genetics of Cancer." Grand Rounds, Department of Medicine, Mercy Medical Center, Rockville Centre, NY; October, 2000.



"Can Molecular Markers Improve Risk Factor Determinations and Thereby Dictate Treatment and Improve Survival?", Plenary Session on Endometrial Cancer, VIII Meeting of the International Gynecologic Cancer Society, Buenos Aires, Argentina; October, 2000.

"Hereditary Ovarian Cancer: What We Know." Helene Harris Memorial Trust 8<sup>th</sup> International Forum on Ovarian Cancer, Houston, TX; March, 2001.

"Genetic Analysis of Ovarian Carcinoma Histogenesis." Gusberg Distinguished Lectureship in Gynecologic Oncology, Mt. Sinai Medical Center, New York, NY; April, 2001.

"Breast and Ovarian Cancers: Basic Science." A Comprehensive Review of Clinical Cancer Genetics, American Society of Clinical Oncology Annual Meeting, San Francisco, CA; May, 2001.

"Molecular Genetics of Hereditary Gynecologic and Breast Cancers: Clinical Implications." Grand Rounds, Department of Medicine, St. Clare's Medical Center, NJ; May, 2001.

"Molecular Biology of Gynecologic Cancers: Clinical Applications." Speaker of the Royal College of Physicians and Surgeons of Canada, Society of Gynecologic Oncologists of Canada Annual Meeting, St. John's, Newfoundland, Canada; June, 2001.

"Molecular Genetics of Hereditary Ovarian Cancer: Clinical Applications." Canadian Federation of Biological Sciences Annual Meeting, Ottawa, Canada; June, 2001.

"Molecular Genetics of Hereditary Ovarian Cancer: Translational Applications." NCI/Center for Cancer Research Grand Rounds, Bethesda, MD; July, 2001.

"Molecular Genetics of Hereditary Gynecologic Cancers: Clinical Implications. Grand Rounds, Department of Obstetrics and Gynecology, Long Island Hospital, Brooklyn, NY; October, 2001.

"Can Clinical Problems in Ovarian Cancer be Solved in the Laboratory?" Visiting Professorship, Department of Obstetrics and Gynaecology, University of Toronto, Toronto, Canada; October, 2001.

"Molecular Genetics of Hereditary Gynecologic and Breast Cancers: Clinical Implications." Grand Rounds, Department of Obstetrics and Gynecology, Columbia University, New York; March, 2002.

“Molecular Genetics of Hereditary Gynecologic Cancers.” Postgraduate Course of Clinical Usefulness of Genetic Testing in Gynecologic Oncology. Society of Gynecologic Oncologists Annual Meeting, Miami Beach, FL; March, 2002.

“Cancer Genetics.” Course on Molecular Oncology, New York University, New York; March, 2002.

“Genetic Analysis of Ovarian Carcinoma Histogenesis.” Conference on Ovarian Cancer and High-Risk Women: Implications of Screening, Prevention, and Early Detection, University of Pittsburgh, Magee-Women’s Hospital, Pittsburgh, PA; May, 2002.

“Basic Science of Breast and Ovarian Cancer.” Comprehensive Course on Clinical Cancer Genetics, American Society of Clinical Oncology Annual Meeting, Orlando, FL, May, 2002.

“Toward a Molecular Classification of Endometrial Carcinoma.” Education Session on Endometrial Carcinoma, American Society of Clinical Oncology Annual Meeting, Orlando, FL; May, 2002.

“Hereditary Gynecologic Cancers: Clinical Implications.” National Corporate Medical Associates Annual Meeting, Memorial Sloan-Kettering Cancer Center, New York, NY; June, 2002.

“Molecular Genetics of Hereditary Ovarian Cancer.” Third Annual International Conference on Ovarian Cancer, MD Anderson Cancer Center, Houston, TX; September, 2002.

“Molecular Biology of Ovarian Cancer: From Pathogenesis to Treatment.” Symposium on Ovarian Cancer, International Gynecologic Cancer Society Biennial Meeting, Seoul, Korea; October, 2002.

“Histogenesis of Ovarian Cancer.” The Ethel N. Ruvelson Lecture in Ovarian Cancer, 33<sup>rd</sup> Annual Autumn Seminar in Obstetrics and Gynecology, University of Minnesota, Minneapolis, MN; October, 2002.

“Hereditary Gynecologic Cancers: What We Know.” Society of Gynecologic Oncologists Winter Meeting, Breckenridge, CO; March, 2003.

“Genetic Analysis of Ovarian Carcinoma Histogenesis.” Helene Harris Memorial Trust 9<sup>th</sup> Biennial Forum on Ovarian Cancer, Stratford-upon-Avon, United Kingdom; March, 2003.

“Cáncer de Ovario: Historia Natural y Biología Molecular.” Cánceres de Próstata, Mama y Ovario: Tumores Hormono-Dependientes, Universidad Internacional Menéndez Pelayo, Santander, Spain; July, 2003.

“Gynecologic Tumors.” Session on New Directions in Cancer, AACR Annual Meeting, Washington, DC; July, 2003.

“Molecular Genetics of Hereditary Gynecologic and Breast Cancers: Clinical Implications.” Hoag Cancer Center Grand Rounds, Newport Beach, CA; July, 2003.

“Genetic Analysis of Ovarian Carcinoma Histogenesis.” Grand Rounds, Department of Pathology, Yale-New Haven Hospital, New Haven, CT; September, 2003.

“Gene Silencing by Estrogen Receptor-Dependent Promoter Methylation.” e.hormone 2003, 5<sup>th</sup> Annual Conference on Environmental Estrogens. Tulane University, New Orleans, LA; October, 2003.

“Genetics of Hereditary Breast and Gynecologic Cancers: Clinical Implications.” 5<sup>th</sup> Annual Kimmel Cancer Center Hereditary Cancer Conference. Thomas Jefferson University, Philadelphia, PA; November, 2003.

Distinguished Visiting Professorship. “Genetic Analysis of Ovarian Carcinoma Histogenesis. Department of Pathology, Johns Hopkins University, Baltimore, MD; November, 2003.

“Genetic Analysis of Ovarian Carcinoma Histogenesis.” 19<sup>th</sup> Annual Ella T. Grasso Memorial Conference. University of Connecticut Health Center, Hartford, CT; November, 2003.

The 13<sup>th</sup> Annual Per Kolstad Memorial Lecture. “Genetics of Hereditary Ovarian Cancer: Clinical Implications.” The Norwegian Radium Hospital, Oslo, Norway; December, 2003.

“Genetic Analysis of Ovarian Carcinoma Histogenesis.” Medical Oncology and Ovarian Cancer Research Program Seminar Series, Fox Chase Cancer Center, Philadelphia, PA; January, 2004.

“BRCA - A Paradigm for Hereditary Cancer Predisposition.” Postgraduate Course on “Genetics for Gynecologic Oncologists”, Society for Gynecologic Oncologists Annual Meeting, San Diego, CA; February, 2004.

“Role of Gene Expression Profiling in Distinguishing Biologically and Clinically Distinct Subclasses of Endometrial Carcinoma.” Gynecologic Cancer Models, Mouse Models of Human Cancers Consortium (NCI) Meeting, San Juan, Puerto Rico; February, 2004.

“Human Cancer Genetics.” Course on Molecular Oncology, New York University, New York, NY; February, 2004.

“Genetic Analysis of Ovarian Carcinoma Histogenesis.” Mayo Oncology Society, Rochester, MN; March, 2004.

“Ovarian Cancer - New Concepts in Organ-Site Research.” American Association for Cancer Research Annual Meeting, Orlando, FL; March, 2004.

“Insights into Biology and Clinical Behavior of Endometrial Carcinoma through Comprehensive Gene Expression Profiling.” Symposium on Ovarian Cancer and Other Gynecologic Malignancies, New York, NY; April, 2004.

“Genetics of Hereditary Gynecologic Cancers.” American Society of Clinical Oncology Annual Meeting, ASCO/SGO Special Session on Clinical Management of Patients with Hereditary Predisposition to Gynecologic Cancers, New Orleans, LA; June, 2004.

“Gene Silencing through Estrogen Receptor Mediated Promoter Methylation.” Gordon Research Conference on Reproductive Tract Biology, New London, CT; June, 2004.

“Genetic Analysis of Ovarian Carcinoma Histogenesis.” Third Early Detection Research Network Scientific Workshop, Bethesda, MD; June, 2004.

“Stratification of Intermediate Risk Disease by Gene Expression Profiling.” 2<sup>nd</sup> Annual Uterine Cancer Biology Symposium, MD Anderson Cancer Center, Houston, TX; September, 2004.

“Is There a Molecular Basis for the Developmental Estrogenization Syndrome?” e.hormone 2004 Conference, New Orleans, LA; October, 2004.

“Genetic Analysis of Ovarian Carcinoma Histogenesis.” Grand Rounds, Dana-Farber/Massachusetts General Hospital, Boston, MA; November, 2004.

“Genetic Analysis of Ovarian Carcinoma Histogenesis.” Grand Rounds, Curtis and Elizabeth Anderson Cancer Institute at Memorial Health University Medical Center, Savannah, GA; December, 2004.

Chair, “Postgraduate Course on Molecular Biology for Gynecologic Oncologists.” Society for Gynecologic Oncologists Annual Meeting, Miami Beach, FL; March, 2005.

“Genetics of the Early Natural History of Ovarian Cancer.” Helene Harris Memorial Trust 10<sup>th</sup> Annual Biennial International Forum on Ovarian Cancer, Washington, DC; April, 2005.

“Genetic Analysis of Ovarian Carcinoma Histogenesis.” Elkin Cancer Biology Seminar Series, Winship Cancer Institute, Emory University School of Medicine, Atlanta, GA; March, 2005.

“Microarray Technology in Gynecologic Cancer Research.” 2<sup>nd</sup> International Symposium on Ovarian Cancer and Other Gynecologic Malignancies, New York, NY; April, 2005.

“Hereditary Ovarian Cancer.” Postgraduate Course on Gynecologic Cancer 2005, Medical College of Georgia/Curtis and Elizabeth Anderson Cancer Institute, Savannah, GA; April, 2005.

“Role of Defective DNA Repair in Gynecologic Tumorigenesis.” Lynne Cohen Symposium on the Emerging Role of Screening and Prevention in Women’s Cancers, NYU University School of Medicine, New York, NY; April, 2005.

“Genetic Analysis of Ovarian Carcinoma Histogenesis.” Multidisciplinary International Conference on Gynecologic Cancer, Bologna, Italy; June, 2005.

“Gene Silencing through Estrogen Receptor-Mediated Promoter Hypermethylation.” Biomedical Research Seminar Program, Mercer University School of Medicine, Macon GA; September, 2005.

“Treatment of Hereditary Ovarian Cancer: Clinical and Experimental Approaches.” And “Haploinsufficiency: Is it Important?” International Symposium on *BRCA*: Today and Tomorrow, Montréal, Canada; October, 2005.

“Opening Key Note Address: Genetic Analysis of Ovarian Carcinoma Histogenesis.” Symposium on Ovarian Cancer: Prevention and Detection of the Disease and its Recurrence. University of Pittsburgh Cancer Institute, Pittsburgh, PA; October, 2005.

“Genetic Analysis of Ovarian Carcinoma Histogenesis.” Grand Rounds, Department of Pathology and Laboratory Medicine, MD Anderson Cancer Center, Houston, TX; January, 2006.

“Cancer Genetics.” Course on Molecular Oncology, New York University School of Medicine, New York, NY; March, 2006.



“Genome-Based Laboratory Approaches to Advancing the Practice of Gynecologic Oncology.” Postgraduate Course on Translational Research, Society for Gynecologic Oncologists Annual Meeting, Palm Springs, CA; March, 2006.

“Translational Research.” Memorial Health University Medical Center First Resident Alumni CME Program, Savannah, GA; June, 2006.

“Molecular Medicine.” Department of Internal Medicine, Memorial Health University Medical Center, Savannah, GA; August, 2006.

“Molecular Basis of Improved Survival in *BRCA*-Linked Ovarian Cancers.” 11<sup>th</sup> Biennial Meeting of the International Gynecologic Cancer Society, Santa Monica, CA; October, 2006.

“Genetic Analysis of Ovarian Carcinoma Histogenesis.” Winter Symposium, Department of Obstetrics and Gynecology, Rambam Health Care Campus, Haifa, Israel; January, 2007.

“Functional Analysis of the CA125 (MUC16) Gene Product in Ovarian Tumorigenesis.” Helene Harris Memorial Trust 11<sup>th</sup> Biennial International Forum on Ovarian Cancer, Lake Como, Italy; March, 2007.

Discussant, Focused Plenary Session on Translational Research in Ovarian Cancer. Society of Gynecologic Oncologists Annual Meeting, San Diego, CA; March, 2007.

“Innovative Cancer Research Activities in Georgia.” Georgia Cancer Summit, Atlanta, GA; January, 2008.

“Applications of Genomics/Proteomics Technologies to Gynecologic Cancers?” Gynecologic Oncology Group Scientific Session on “Genomics and Proteomics: The Future is Now”. GOG Semi-Annual Meeting, San Diego, CA; January, 2008.

“Molecular Evolution of Ovarian Cancer.” 1<sup>st</sup> Ovarian Cancer Action International Conference, London, United Kingdom; March, 2008.

“Genetics 101.” Sunrise Postgraduate Session, Society of Gynecologic Oncologists Annual Meeting, Tampa, FL; March, 2008.

Discussant, Focused Plenary Session on Translational Research, Society of Gynecologic Oncologists Annual Meeting, Tampa, FL; March, 2008.

“Genetic Profiling of Endometrial Cancers.” Fifth International Symposium on Ovarian Cancer and Gynecologic Malignancies, New York, NY; March, 2008.

“Cancer Genetics.” Grand Rounds, Department of Internal Medicine, Memorial University Medical Center, Savannah, GA; April, 2008.

“The Future of Healthcare: Genetic Medicine.” Annual Meeting of the Coastal Empire Health Underwriters Association, Savannah, GA; May, 2008.

“Relevance of Tumor Biology to Prevention and Diagnosis.” International Symposium on Hereditary Breast and Ovarian Cancer: Risks and Challenges, Bari, Italy; September, 2009.

“Whence Epithelial Ovarian Carcinoma?” Robert F. Ozols Symposium on Gyn Cancer: Gyn Cancers – the Next 25 Years, Philadelphia, PA; September, 2009.

Session Chair. Opening Plenary Session I; Interactive Session: “Hereditary Gynecologic Cancers.” 13<sup>th</sup> Biennial Meeting of the International Gynecologic Cancer Society, Prague, Czech Republic; October, 2010.

“Whence Epithelial Ovarian Carcinoma?” Ovarian Cancer National Alliance Regional Symposium; Radnor, PA; November, 2010.

“The Origin of Epithelial Ovarian Carcinoma: New Insights.” Omniprex 2011 Ovarian Cancer Course; Philadelphia, PA; April, 2011.

“Whence Epithelial Ovarian Carcinoma?” Grand Rounds, Department of Obstetrics and Gynecology, Michigan State University School of Medicine; Grand Rapids, MI; May, 2011.

“Low Grade Serous Carcinomas.” From Molecular Information to Cancer Medicine - NCI Translational Science Meeting 2011, Washington, DC; July, 2011.

“The Vision and the Reality: One Cancer Center’s Journey toward Genomic Medicine.” Keynote Session, The Clinical Genome Conference, San Francisco, CA; June, 2012.

“The Vision and the Reality: One Cancer Center’s Journey toward Genomic Medicine.” Keynote Session, Ion Torrent User’s Group Meeting, Baltimore, MD; March, 2013.

“Cancer Genetics and the Evolution of Precision Medicine.” Memorial Sloan-Kettering Cancer Center, New York, NY; May, 2013.

Co-Organizer, “Ovarian Cancer: Developing Research-Based Public Messaging on Early Detection and Screening.” The Banbury Center, Cold Spring Harbor, NY; October, 2013.

“Cancer Genetics and the Evolution of Precision Medicine.” Grand Rounds, Department of Obstetrics and Gynecology, New York University School of Medicine, New York, NY; February, 2014.

“Defective Homologous Recombination and Therapeutic Opportunities in Ovarian Cancer.” First Annual Meeting of International Ovarian Cancer Consortium: Tumor Microenvironment and Drug Discovery, University of Oklahoma Health Sciences Center, Oklahoma City, OK; February, 2014.

“Ethical, Legal, and Social Implications of Clinical Next-Generation Sequencing.” Cancer Prevention and Control Program, Fox Chase Cancer Center, Philadelphia, PA; March, 2014.

“Lecturette: The Use of “omics”-Based Predictors in Clinical and Translational Research.” Society of Gynecologic Oncology Annual Meeting, Tampa, FL; March, 2014.

“Genetic Solutions to the Cancer Problem: A Personal Perspective.” The Jackson Laboratory for Genomic Medicine, Farmington, CT; August, 2014.

Keynote Presentation: “The Vision and the Reality: One Cancer Center’s Journey toward Genomic Medicine.” Seventh Annual Predictive Cancer Biomarkers Conference, Washington, DC; August, 2014.

“The Vision and the Reality: One Cancer Center’s Journey toward Genomic Medicine.” Third Annual Genomics in Medicine Symposium – Molecular Medicine Tri-Conference 2015, San Francisco, CA; February, 2015.

Panel Member, “Targeted Oncology”. BIO 2015 International Conference, Philadelphia, PA; June, 2015.

“The Vision and the Reality: One Cancer Center’s Journey toward Genomic Medicine.” 8<sup>th</sup> Annual Predictive Cancer Biomarkers Conference, Washington, DC; August, 2015.

“Cancer Genetics and the Evolution of Precision Medicine.” Grand Rounds, Broward Health Medical Center, Ft. Lauderdale, FL; March, 2016.

“Genetics of Women’s Cancers: Advances through Genomic Medicine.” Fifth Annual Omar Pasalodos, MD, Memorial Lecture, Miami, FL; April, 2016.

“Advances in Genomic Medicine: Focus on Head and Neck Cancers.” Fifth Annual Head and Neck Cancer Symposium, Miami, FL; April, 2016.

“Cancer Genetics in the Primary Care Setting.” The International Symposium on Primary Care, Miami Beach, FL; July, 2016.

“Genomic Predisposition to Breast Cancer.” Fourth Annual John M. Cassel, MD, Memorial Breast Cancer Symposium, Miami, FL; September, 2016.

“Updates on the UKCTOCS Trial.” Ovarian Cancer State-of-the-Art Conference, Memorial Sloan-Kettering Cancer Center, New York, NY; October, 2016.

“Genetics of Cancer: New Opportunities through Genomic Medicine.” Miami Medical Forum, Miami, FL; October, 2016.

“Cancer Genetics and the Evolution of Precision Medicine.” Presidential Plenary Session, International Gynecologic Cancer Society Biennial Meeting, Lisbon, Portugal; October, 2016.

“Genetic Predisposition to Cancer.” Baptist Health South Florida Research Summit: Bringing Cancer Research to the Community, Miami, FL; November, 2016.

“Germline Testing Meets Genomic Testing: How to Sort It Out.” Second Annual West Cancer Center Oncology Conference: Collaboration for the Future Cure: Precision Medicine and Immuno-Oncology, Memphis, TN; November, 2016.

“Genetics of Women’s Cancers: Advances through Genomic Medicine.” Second Annual MSK Cancer Alliance Scientific Symposium, Miami, FL; January, 2017.

“Precision Medicine in Cancer Care: Global Challenges and Opportunities.” Enmore Bio Conference, Nanjing, China; February, 2017.

“Genetics of Women’s Cancers: Advances through Genomic Medicine.” Grand Rounds, Department of Obstetrics and Gynecology, Lehigh Valley Health Network, Allentown, PA; May, 2017.

“How to Interpret Tumor Genomics for the Oncologist.” Education Session on Cascade Testing: What to Do When Ascertaining Germline Mutations from Tumor and Other Genomic Testing. American Society of Clinical Oncology Annual Meeting, Chicago, IL; June, 2017.

“Genetics of Women’s Cancers: Advances through Genomic Medicine.” President’s Guest Speaker, Miami Obstetrical and Gynecological Society, Miami, FL; September, 2017.

“Genetics of Women’s Cancers: Advances through Genomic Medicine.” Grand Rounds, Simon Cancer Center, Indiana University, Indianapolis, IN; October, 2017.

“Genomics and Pediatric Malignancies.” Kids with Cancer Symposium, Miami, FL; December, 2017.

“The Challenges and Rewards for Bringing AI into the Clinic for Health and Disease Management.” Panel Discussion, Precision Medicine World Conference, Mountain View, CA; January, 2018.

“Genomics Revolution in Cancer Care.” Al and Janie Nahmad Speaker Series: Thought Leaders in Medicine, Miami, FL; April, 2018.

“Cancer Genomics.” Baptist Health International Videoconference, Miami, FL; September, 2018.

“Estrogen and Cancer.” Visiting Professorship, Department of Obstetrics and Gynecology, University of Chicago, Chicago, IL; September, 2018.

“BRCA, Genetics, and Genomics: Role in Ovarian Cancer.” Fight N Heal Teal Symposium, Miami, FL; October, 2018.



Ad Hoc Reviewer:

American Journal of Human Genetics  
American Journal of Obstet and Gynecol  
American Journal of Pathology  
Annals of Surgical Oncology  
BBA Reviews on Cancer  
BMC Cancer  
Breast Cancer Research and Treatment  
British Journal of Cancer  
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European Journal of Cancer  
Genes, Chromosomes, and Cancer  
Genomics  
Gynecologic Oncology  
International Journal of Cancer  
International Journal of Gynecologic Cancer  
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Journal of Molecular Endocrinology  
Journal of the National Cancer Inst  
Lancet  
Molecular Cancer Therapeutics  
Molecular Carcinogenesis  
Molecular Endocrinology  
Molecular Pharmacology  
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Nature Communications  
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Nature Reviews Cancer  
New England Journal of Medicine  
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# **EXHIBIT B**

Testifying History for Jeff Boyd, Ph.D.

**University of Miami v. Agency for Health Care Administration and Baptist  
Hospital of Miami, Inc.**

State of Florida Division of Administrative Hearings  
Case No. 16-001698CON

**University of Miami v. Baptist Hospital of Miami, Inc., and Agency for Health  
Care Administration**

State of Florida Division of Administrative Hearings  
Case No. 17-005301CON

# Exhibit Z

Jeffrey A. Boyd, Ph.D.

Page 1

UNITED STATES DISTRICT COURT  
DISTRICT OF NEW JERSEY

IN RE: JOHNSON & )  
JOHNSON TALCUM POWDER )  
PRODUCTS MARKETING )  
SALES PRACTICES AND ) MDL 16-2738  
PRODUCT LIABILITY ) (FLW)(LHG)  
LITIGATION )  
\_\_\_\_\_)  
THIS DOCUMENT )  
PERTAINS TO ALL CASES )

MONDAY, APRIL 8, 2019

CONFIDENTIAL - PURSUANT TO PROTECTIVE ORDER

- - -

Videotaped deposition of Jeffrey A.  
Boyd, Ph.D., held at the offices of Shook,  
Hardy & Bacon LLP, 201 South Biscayne  
Boulevard, Suite 3200, Miami, Florida,  
commencing at 9:03 a.m., on the above date,  
before Carrie A. Campbell, Registered  
Diplomate Reporter and Certified Realtime  
Reporter.

- - -

GOLKOW LITIGATION SERVICES  
877.370.3377 ph | 917.591.5672 fax  
deps@golkow.com

Jeffrey A. Boyd, Ph.D.

Page 2	Page 4
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Page 3	Page 5
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Jeffrey A. Boyd, Ph.D.

<p style="text-align: right;">Page 6</p> <p>1 Boyd 19 GYN-18-1020: Final Decision 274 Letter to Dr. Saed</p> <p>2 Boyd 20 Mg3Si2O5(OH)4 283</p> <p>3 Boyd 21 "Identifying postmenopausal 299 4 women at elevated risk for epithelial ovarian cancer," 5 Urban, et al.</p> <p>6 Boyd 22 "Role of CA125 in predicting 303 7 ovarian cancer survival -a review of the epidemiological 8 literature," Gupta, et al.</p> <p>9 Boyd 23 "Tumor-associated 307 10 autoantibodies as early detection markers for ovarian 11 cancer? A prospective evaluation," Kaaks, et al.</p> <p>12 Boyd 24 "Ovarian cancer screening and 310 13 mortality in the UK Collaborative Trial of Ovarian Cancer Screening (UKTOCS): A 14 randomised controlled trial," Jacobs, et al.</p> <p>15 Boyd 25 "Early Detection of Ovarian 314 Cancer," Elias, et al.</p> <p>16 Boyd 26 "The MPO-463 G&gt; A polymorphism 326 17 and cancer risk: A meta-analysis based on 43 18 case-control studies," Chu, et al.</p> <p>19 Boyd 27 "Opportunities and challenges 344 20 in ovarian cancer research, a perspective from the 11th 21 Ovarian cancer action-HHMT Forum, Lake Como, March 2007," 22 Gynecologic Oncology 23 24 25</p>	<p style="text-align: right;">Page 8</p> <p>1 DIRECT EXAMINATION</p> <p>2 QUESTIONS BY MR. RESTAINO:</p> <p>3 Q. Good morning, Dr. Boyd.</p> <p>4 A. Good morning.</p> <p>5 Q. Before the deposition started,</p> <p>6 I introduced myself, but for the record, my</p> <p>7 name is John Restaino. And stating the</p> <p>8 obvious, I'm representing the plaintiffs in</p> <p>9 this litigation.</p> <p>10 It's my understanding that</p> <p>11 you've had your deposition taken at least</p> <p>12 twice before; is that correct?</p> <p>13 A. Yes.</p> <p>14 Q. So you're vaguely aware of the</p> <p>15 rules that we'll be operating under today; is</p> <p>16 that correct?</p> <p>17 A. Yes.</p> <p>18 Q. Okay. In essence, this is not</p> <p>19 a memory test, so if you need to refer to a</p> <p>20 document, it's open book.</p> <p>21 It's not a physical test, so</p> <p>22 we'll try to take a take break about every</p> <p>23 hour, hour and 15 minutes or so. However, in</p> <p>24 between breaks, if you need to take a break</p> <p>25 for whatever reason, assuming there isn't a</p>
<p style="text-align: right;">Page 7</p> <p>1 VIDEOGRAPHER: We are on the</p> <p>2 record. My name is Devyn Mulholland.</p> <p>3 I'm a videographer with Golkow</p> <p>4 Litigation Services.</p> <p>5 Today's date is April 8, 2019.</p> <p>6 The time is 9:03 a.m.</p> <p>7 This video deposition is being</p> <p>8 held in Miami, Florida, in the matter</p> <p>9 of talcum powder litigation.</p> <p>10 The deponent is Jeff Boyd,</p> <p>11 Ph.D.</p> <p>12 Counsel will be noted on the</p> <p>13 stenographic record.</p> <p>14 The court reporter is Carrie</p> <p>15 Campbell, who will now swear in the</p> <p>16 witness.</p> <p>17</p> <p>18 JEFFREY A. BOYD, Ph.D.,</p> <p>19 of lawful age, having been first duly sworn</p> <p>20 to tell the truth, the whole truth and</p> <p>21 nothing but the truth, deposes and says on</p> <p>22 behalf of the Plaintiffs, as follows:</p> <p>23</p> <p>24</p> <p>25</p>	<p style="text-align: right;">Page 9</p> <p>1 question pending, just let us know and we'll</p> <p>2 accommodate that.</p> <p>3 A. Thank you.</p> <p>4 Q. Understand?</p> <p>5 There are times when, based</p> <p>6 upon my question -- this is extremely rare --</p> <p>7 but Jessica may object to my questions,</p> <p>8 because usually my questions are perfect.</p> <p>9 That's -- unless counsel instructs you not to</p> <p>10 answer, it's the lawyers, in essence,</p> <p>11 protecting the record for each perspective.</p> <p>12 I don't get to say "objective,"</p> <p>13 {sic} but if I ask you a particular question</p> <p>14 and then I don't think you answered my</p> <p>15 question, I may say "move to strike as</p> <p>16 unresponsive." I'm not being rude. Once</p> <p>17 again, we're making the record.</p> <p>18 Do you understand?</p> <p>19 A. Yes.</p> <p>20 Q. Okay. And with that, so far</p> <p>21 we're off to a good start. There's the</p> <p>22 lovely lady to your right, my left, and she's</p> <p>23 going to try to take down everything that we</p> <p>24 each say.</p> <p>25 If two individuals are talking</p>

3 (Pages 6 to 9)



Jeffrey A. Boyd, Ph.D.

<p style="text-align: right;">Page 10</p> <p>1 at a bar, having a drink, it's very common to</p> <p>2 step on each other's lines. Not being rude,</p> <p>3 just normal discourse, but it'll make her</p> <p>4 life a little tougher. So if you try to</p> <p>5 listen for the question mark at the end of my</p> <p>6 questions, and I'll try to listen to the</p> <p>7 period. And if I step on your answer, it's</p> <p>8 not intentional and I'll apologize, but let's</p> <p>9 try to keep it clean for her.</p> <p>10 Make sense?</p> <p>11 A. Fair enough.</p> <p>12 Q. If I ask you a question and you</p> <p>13 answer it, we will assume you understood the</p> <p>14 question. So therefore, if you don't</p> <p>15 understand the question, please let me know,</p> <p>16 and I'll try to rephrase it in a more</p> <p>17 understandable manner.</p> <p>18 Understood?</p> <p>19 A. Yes.</p> <p>20 Q. And no one in the room wants</p> <p>21 you to guess today, though there may be times</p> <p>22 when an estimate is in order. And I'm not</p> <p>23 going to insult your intelligence as to the</p> <p>24 difference between a guess and an estimate.</p> <p>25 I'm sure you know that.</p>	<p style="text-align: right;">Page 12</p> <p>1 to say, he doesn't have those</p> <p>2 responses.</p> <p>3 MR. RESTAINO: Yeah.</p> <p>4 QUESTIONS BY MR. RESTAINO:</p> <p>5 Q. And if you notice again, on the</p> <p>6 third to last page there's some other</p> <p>7 documents that are attached to this which</p> <p>8 I've marked -- this is the Johnson &amp; Johnson</p> <p>9 response to the notice, production-marked as</p> <p>10 number 2, and there's a supplemental</p> <p>11 materials considered, and the page after that</p> <p>12 a correspondence from you to a Jessica</p> <p>13 Miller, and then on the last page an invoice</p> <p>14 with a redaction in the center.</p> <p>15 Do you see that, sir?</p> <p>16 A. Yes.</p> <p>17 Q. And have you seen this before?</p> <p>18 A. Yes.</p> <p>19 Q. Okay. When did you see this,</p> <p>20 other than this morning?</p> <p>21 A. Well, if we go back to the</p> <p>22 third from last page, we -- I looked at this</p> <p>23 briefly yesterday afternoon.</p> <p>24 Q. Okay.</p> <p>25 A. And, of course, the invoice and</p>
<p style="text-align: right;">Page 11</p> <p>1 So in essence, no guessing</p> <p>2 today. Just if you're not sure, just let us</p> <p>3 know or give us your best estimate.</p> <p>4 Do you understand that?</p> <p>5 A. Yes.</p> <p>6 Q. Before the deposition started,</p> <p>7 I premarked a couple of exhibits to save a</p> <p>8 little bit of time. And the first one is the</p> <p>9 notice of your deposition. And I'm going to</p> <p>10 hand you this now.</p> <p>11 (Boyd Exhibits 1 and 2 marked</p> <p>12 for identification.)</p> <p>13 QUESTIONS BY MR. RESTAINO:</p> <p>14 Q. And, Dr. Boyd, have you seen</p> <p>15 this before?</p> <p>16 A. I don't remember seeing it, no.</p> <p>17 Q. Okay. In response to it, and</p> <p>18 it might be a little easier to go along, the</p> <p>19 attorneys for Johnson &amp; Johnson has filed a</p> <p>20 response to that. And glance through it.</p> <p>21 Not only are there responses, but if you see</p> <p>22 on the third to last page there's</p> <p>23 supplemental materials considered on this</p> <p>24 form here. I'm going to hand them -- sorry.</p> <p>25 MS. MILLER: Yeah, I was going</p>	<p style="text-align: right;">Page 13</p> <p>1 the accompanying documentation underlying the</p> <p>2 invoice, I obviously saw it on or about</p> <p>3 February 25th.</p> <p>4 Q. Okay. And you said that if we</p> <p>5 go back to the third from last page, "I</p> <p>6 looked at this briefly yesterday afternoon."</p> <p>7 And this is a supplemental materials</p> <p>8 considered, correct? On the third to last</p> <p>9 page?</p> <p>10 A. Yes, you've read it correctly.</p> <p>11 Q. Did you type this up?</p> <p>12 A. No.</p> <p>13 Q. Do you know who typed it up?</p> <p>14 A. No.</p> <p>15 Q. Have you, in fact, reviewed the</p> <p>16 documents that are listed on this page?</p> <p>17 A. At least in very cursory</p> <p>18 fashion, yes.</p> <p>19 Q. Each and every one of them?</p> <p>20 A. Yes.</p> <p>21 (Boyd Exhibit 3 marked for</p> <p>22 identification.)</p> <p>23 QUESTIONS BY MR. RESTAINO:</p> <p>24 Q. I'm also going to mark -- or I</p> <p>25 have marked as number 3 the testifying</p>

4 (Pages 10 to 13)

Jeffrey A. Boyd, Ph.D.

<p style="text-align: right;">Page 14</p> <p>1 history for Jeff Boyd, Ph.D.  2 Have you seen this before?  3 A. Yes.  4 Q. And is that accurate?  5 MS. MILLER: So I would like to  6 just say something because obviously  7 my paralegal typed this up, and she  8 should have put within the last -- she  9 should have specified within how many  10 years. I mean, this was done pursuant  11 to the Federal Rules.  12 I just didn't want it to  13 suggest that it's the full testifying  14 history.  15 MR. RESTAINO: Let the record  16 denote that, and I assumed that.  17 MS. MILLER: Okay.  18 MR. RESTAINO: Thank you,  19 Jessica.  20 QUESTIONS BY MR. RESTAINO:  21 Q. Is that accurate for your  22 deposition in the last four years?  23 A. My testifying history?  24 Q. Yes.  25 A. Yes.</p>	<p style="text-align: right;">Page 16</p> <p>1 had one as well and so sought to prevent the  2 development of the aforementioned bone marrow  3 transplant unit at the Miami Cancer Institute  4 with some type of -- some type of legal suit,  5 for lack of a better term.  6 Q. Okay.  7 A. Which landed us in what I  8 recall as an administrative-type litigation  9 as opposed to, for example, a criminal or --  10 Q. Understood.  11 A. -- some other type.  12 And we were deposed and  13 appeared before an administrative court judge  14 in Tallahassee.  15 Q. When you're saying "we," were  16 you a witness, a party or an expert or  17 something else in that litigation?  18 A. I would have to say this being  19 a very new kind of litigation to me, I would  20 have classified myself -- I seem tongue --  21 tongue-tied this morning, I'm sorry -- as a  22 witness.  23 Q. Okay. Essentially the same  24 thing for the second one, the -- again, I see  25 a State of Florida Division of Administrative</p>
<p style="text-align: right;">Page 15</p> <p>1 Q. The first one, University of  2 Miami versus Agency for Health Care  3 Administration and Baptist Hospital of Miami,  4 Inc., what were the underlying facts of that  5 case, if you recall?  6 A. The Miami Cancer Institute and  7 Baptist Hospital of Miami, Inc., were filing  8 a certificate of need for a bone marrow  9 transplant unit at the Miami Cancer Institute  10 through the Florida Department of Health or  11 the Agency for Health Care Administration. I  12 think they're closely linked, to the best of  13 my knowledge. And the state, the agency, the  14 Florida Agency for Health Care  15 Administration, the Florida Department of  16 Health, to the best of my knowledge, in a CON  17 case, granted or allowed the certificate of  18 need, thus allowing us to establish a bone  19 marrow transplant unit at the Miami Cancer  20 Institute.  21 And to the best of my  22 knowledge, the University of Miami,  23 specifically the Sylvester Cancer Center,  24 took issue with Miami Cancer Institute having  25 a bone marrow transplant unit because they</p>	<p style="text-align: right;">Page 17</p> <p>1 hearings, so similar type of hearing?  2 A. It was basically a ditto.  3 Q. Okay.  4 A. We lost, "we" being Miami  5 Cancer Institute, Baptist Hospital, the first  6 case.  7 Lather, rinse, repeat. We  8 filed another CON that was approved by the  9 State. University of Miami sued. Went back  10 to the administrative court with a different  11 judge, and he ruled in our favor.  12 Q. And you had a similar --  13 A. We now have a bone marrow  14 transplant unit at the Miami Cancer  15 Institute.  16 I'm sorry for interrupting you.  17 Q. And I'm sorry for interrupting  18 you.  19 And essentially the same role  20 in the second proceeding, as a witness?  21 A. Yes.  22 Q. Okay. Now, my understanding is  23 you're charging \$600 an hour for the document  24 type of review in this litigation?  25 A. Yes.</p>

5 (Pages 14 to 17)

Jeffrey A. Boyd, Ph.D.

<p style="text-align: right;">Page 18</p> <p>1 Q. And you're charging \$1,200 per 2 hour for deposition and other testimony? 3 A. Yes. 4 Q. When is the last time, if ever, 5 you've been an expert witness in a 6 litigation? 7 A. Other than for my employer? 8 Q. Yes. 9 A. And here we're going to get 10 into the realm of an estimate, I guess. It 11 would have been the late '90s, early 2000s. 12 Q. Okay. Were you charging \$1,200 13 an hour for deposition testimony then? 14 A. My memory is that I was 15 charging 400, 800. 16 Q. Okay. When did you start 17 charging \$1,200 an hour? 18 A. Well, at the beginning of this 19 proceeding. 20 Q. Okay. Today we're going to be 21 here, and as you'll probably hear several 22 times, attorneys from both sides will be 23 asking the videographer how much time is on 24 the tape, because by the Federal Rules we get 25 seven hours of questioning. So you will be</p>	<p style="text-align: right;">Page 20</p> <p>1 correct. 2 Q. Another one of those estimate 3 questions. Can you estimate for us the 4 number of hours you have now between February 5 21st and April 7th? 6 MS. MILLER: Remember not to 7 guess. 8 THE WITNESS: I think a 9 reasonable estimate would be somewhere 10 between 70 and 100 hours. 11 QUESTIONS BY MR. RESTAINO: 12 Q. Okay. And because that's for 13 document review, that would be at the 14 \$600-an-hour rate? 15 A. Yes. 16 (Boyd Exhibit 4 marked for 17 identification.) 18 QUESTIONS BY MR. RESTAINO: 19 Q. Okay. I've now marked as 20 Plaintiff 4 the version of your CV that we've 21 received. 22 To the best of your knowledge, 23 is that a current CV? 24 A. As of February the 4th, 2019, 25 it would certainly have been an accurate,</p>
<p style="text-align: right;">Page 19</p> <p>1 charging Johnson &amp; Johnson the \$1,200 for 2 those seven hours? 3 MS. MILLER: Objection. 4 QUESTIONS BY MR. RESTAINO: 5 Q. \$1,200 an hour for those seven 6 hours? 7 MS. MILLER: Objection. 8 THE WITNESS: Again, I'm sorry, 9 I don't do this a lot. My 10 understanding is that I send an 11 invoice to Ms. Miller, and the one 12 time I've done it, I received a check 13 from Skadden. 14 I honestly don't know how money 15 changes hands in these circumstances, 16 but I will be submitting -- I'm sorry, 17 I will be submitting an invoice to 18 Ms. Miller. 19 QUESTIONS BY MR. RESTAINO: 20 Q. Okay. And the last page of 21 Exhibit 2, I believe, is the invoice between 22 December 18th and February 21st; is that 23 correct? 24 A. It is an invoice for the period 25 between December 18th and February 21st,</p>	<p style="text-align: right;">Page 21</p> <p>1 up-to-date CV. 2 Q. And I will represent to you 3 that I have not added nor taken anything out 4 of your CV. 5 A. Thank you. 6 Q. And I'm sorry, Doctor, you said 7 that it was current as of February 4th. 8 As you sit here today, is there 9 anything that's been -- that needs to be 10 added or any publication that's coming out 11 that's specifically germane to talc, 12 inflammation, ovarian cancer, the reason why 13 we're here? 14 Anything new that will be 15 coming out? 16 MS. MILLER: Objection. 17 THE WITNESS: No. 18 QUESTIONS BY MR. RESTAINO: 19 Q. Okay. You understood that 20 question? 21 Because that wasn't a great 22 question. 23 MS. MILLER: That's why I 24 objected. 25 MR. RESTAINO: Yeah. Let the</p>

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<p style="text-align: right;">Page 22</p> <p>1 record denote that's the first time.</p> <p>2 MS. MILLER: Are you keeping a</p> <p>3 count today?</p> <p>4 THE WITNESS: I understood the</p> <p>5 question.</p> <p>6 QUESTIONS BY MR. RESTAINO:</p> <p>7 Q. Okay.</p> <p>8 A. And I stand behind my answer.</p> <p>9 Q. Now, prior to the deposition</p> <p>10 started, there was a little bit of a</p> <p>11 communication or discussion between yourself</p> <p>12 and Dr. Jennifer Emmel sitting to my right.</p> <p>13 Do you recall meeting with</p> <p>14 Dr. Emmel before?</p> <p>15 A. No.</p> <p>16 Q. Do you have -- if you met with</p> <p>17 an attorney in, say, March of 2017, would you</p> <p>18 keep records of any notes that you took?</p> <p>19 A. Well, that's very hard to say</p> <p>20 because I don't remember meeting with an</p> <p>21 attorney in March of 2017.</p> <p>22 Q. Okay. Fair enough. If you</p> <p>23 don't remember, you don't remember.</p> <p>24 MS. MILLER: We seem to be</p> <p>25 having this issue arise multiple</p>	<p style="text-align: right;">Page 24</p> <p>1 Q. In the request to produce, if</p> <p>2 you look at number 3, Request to Produce</p> <p>3 Number 3 --</p> <p>4 A. Number 3 what?</p> <p>5 Q. On the request to produce,</p> <p>6 which is on Exhibit Number 2. And so you</p> <p>7 have to turn to --</p> <p>8 A. What is number 3 in Exhibit</p> <p>9 Number 2, please?</p> <p>10 MS. MILLER: Wait. So here you</p> <p>11 go, Doctor. There's stickies at the</p> <p>12 bottom of the page. That's Exhibit 2.</p> <p>13 THE WITNESS: Yes.</p> <p>14 MS. MILLER: And he wants you</p> <p>15 to go to request -- this is just all</p> <p>16 like legal garble. It's mumbo jumbo.</p> <p>17 And he wants you to --</p> <p>18 THE WITNESS: I'm just not sure</p> <p>19 what number 3 means. I'm sorry.</p> <p>20 MS. MILLER: Request Number 3.</p> <p>21 THE WITNESS: Okay. So I'm on</p> <p>22 the page.</p> <p>23 QUESTIONS BY MR. RESTAINO:</p> <p>24 Q. Okay. And it asks for your</p> <p>25 complete file or files related to the work</p>
<p style="text-align: right;">Page 23</p> <p>1 times.</p> <p>2 QUESTIONS BY MR. RESTAINO:</p> <p>3 Q. If we look at the -- your</p> <p>4 response, so Exhibit 2, I believe, you see</p> <p>5 that there's specific requests. And I'm not</p> <p>6 going to spend a lot of time going through</p> <p>7 it, but if you start off with Request</p> <p>8 Number 3, your complete file or files.</p> <p>9 Do you have a file in this</p> <p>10 litigation, and if so, have you previously</p> <p>11 produced it to your counsel?</p> <p>12 MS. MILLER: Wait a minute.</p> <p>13 We're not his counsel. We're J&amp;J's</p> <p>14 counsel. So...</p> <p>15 QUESTIONS BY MR. RESTAINO:</p> <p>16 Q. Let me rephrase that by saying</p> <p>17 have you previously produced it to counsel</p> <p>18 for J&amp;J, representing J&amp;J here today?</p> <p>19 A. I'm sorry, but that was a very</p> <p>20 long question, statement.</p> <p>21 Q. Yeah, let me just reask it.</p> <p>22 A. Can we just start over, please?</p> <p>23 Q. Of course.</p> <p>24 A. Perhaps parse the -- I'm sorry,</p> <p>25 perhaps parse the questions?</p>	<p style="text-align: right;">Page 25</p> <p>1 done.</p> <p>2 Have you previously produced to</p> <p>3 counsel for Johnson &amp; Johnson your file or</p> <p>4 files in this regard?</p> <p>5 A. Again, could you repeat the</p> <p>6 question, please?</p> <p>7 Q. Request Number 3 asks for a</p> <p>8 copy of your complete file or files related</p> <p>9 to work on -- concerning talcum powder</p> <p>10 litigation, talcum powder products or talc in</p> <p>11 general.</p> <p>12 Have you produced any such</p> <p>13 files?</p> <p>14 A. No.</p> <p>15 Q. Are there files that you have</p> <p>16 back at your office?</p> <p>17 A. Pertaining to Request Number 3?</p> <p>18 Q. Yes.</p> <p>19 A. No.</p> <p>20 Q. Are there files anywhere else?</p> <p>21 A. No.</p> <p>22 Q. The reason I'm confused is</p> <p>23 because I asked you if you've produced a copy</p> <p>24 of your complete file or files to counsel for</p> <p>25 Johnson &amp; Johnson, and your answer was no.</p>

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<p style="text-align: right;">Page 26</p> <p>1 A. Let's back up a little bit, 2 please. 3 First of all, I have two 4 offices, I have a study at home, and I have 5 no files at either work-related office or in 6 my study at home related to this matter. 7 Q. Okay. 8 MS. MILLER: I think he was 9 saying he didn't produce anything 10 because he didn't have anything. 11 I assume that's what you were 12 saying. That's how I understood it. 13 THE WITNESS: I don't have 14 anything. Certainly I keep records of 15 the time spent researching in order to 16 provide an accurate invoice, but other 17 than that, I have no files. 18 QUESTIONS BY MR. RESTAINO: 19 Q. Okay. Fair enough. 20 If you go down now to Request 21 Number 7, and there it's asking for articles, 22 papers and/or scientific, technical 23 publications written, prepared and/or 24 presented by you or in which you participated 25 in writing, preparing or presenting that</p>	<p style="text-align: right;">Page 28</p> <p>1 A. Yes. 2 Q. Okay. And I can skip a few 3 more. 4 If you skip down to Request 5 Number 15, and I'll wait for you to get 6 there. "All documents related to 7 communications with employees, 8 representatives, editors, or reviewers of any 9 scientific or medical journal which discuss 10 talcum powder products, talc and/or talcum 11 powder." 12 Are there any such documents? 13 A. No. 14 Q. And number 17 is "any slide 15 decks" -- 16 "Slide decks," old term. 17 A. It's a colloquialism. 18 Q. Back in the day. 19 -- "outlines, presentations or 20 other materials you've created or utilized in 21 connection with any presentation on talcum 22 powder, talc, and/or talcum powder products." 23 Do any of those exist? 24 A. No. 25 Q. And can we just have a general</p>
<p style="text-align: right;">Page 27</p> <p>1 relate or concern talcum powder products, 2 talc and talcum powder. 3 And if there are any such 4 publications, articles, papers, have you 5 previously produced them to counsel for 6 Johnson &amp; Johnson? 7 MS. MILLER: Objection. 8 There's a couple of questions embedded 9 in there. It might be better to first 10 ask him if he has them and then if 11 he's produced them, because I think 12 that created a little bit of confusion 13 on the last round of questions. 14 QUESTIONS BY MR. RESTAINO: 15 Q. Okay. Doctor, as per Request 16 Number 7, do you have any "articles, papers, 17 scientific and/or technical publications 18 written, prepared and/or presented by you or 19 in which you participated in writing, 20 preparing or presenting that relate or 21 concern talcum powder products, talc and/or 22 talcum powder"? 23 A. My expert report. 24 Q. Okay. And that would be the 25 totality of it?</p>	<p style="text-align: right;">Page 29</p> <p>1 understanding sitting here in 2019 that slide 2 decks would also consider like PowerPoint 3 presentations? 4 A. That's how I refer to my 5 PowerPoint presentations, yes. 6 Q. You give presentations at 7 medical and/or scientific society meetings or 8 programs? 9 A. Yes. 10 Q. Do you show up with that little 11 round carousel of slides anymore, or do you 12 show up with a PowerPoint? 13 A. A, not for a long time; and B, 14 yes. 15 Q. Okay. If we go to the back of 16 your Exhibit 2 and point out the supplemental 17 materials that were considered, that I 18 believe you testified to that you saw 19 yesterday. 20 A. Yes. 21 Q. Okay. The first one is 22 deposition of Benjamin Neel. 23 Do you know who Dr. Neel is? 24 A. Yes. 25 Q. And that's N-e-e-l.</p>

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<p style="text-align: right;">Page 30</p> <p>1 Prior to this litigation, did 2 you know Dr. Benjamin Neel? 3 MS. MILLER: Objection. 4 THE WITNESS: I still... 5 MS. MILLER: What do you mean 6 by "know"? I mean, that's why I 7 objected to the question. 8 Do you mean know or know of? 9 MR. RESTAINO: Know. 10 MS. MILLER: Okay. 11 THE WITNESS: K-n-o-w? 12 MS. MILLER: Objection. 13 MR. RESTAINO: I'm sorry? 14 THE WITNESS: K-n-o-w? 15 MR. RESTAINO: Please. 16 MS. MILLER: I'm still 17 objecting to that because I don't know 18 what it means. 19 QUESTIONS BY MR. RESTAINO: 20 Q. If you saw Benjamin Neel at an 21 upcoming meeting, is it someone that you 22 would walk to and say, "Ben, how you doing?" 23 and shake his hand? 24 A. No. 25 Q. Okay. Do you know of</p>	<p style="text-align: right;">Page 32</p> <p>1 fellows at the center completed their 2 mandatory two years of research training in 3 my laboratory, and that's when I first met 4 Dr. Saenz. 5 Q. Okay. And number 9 is the 6 expert report of Dr. Saenz. 7 Have you reviewed her expert 8 report? 9 A. Yes. 10 Q. In its totality? 11 MS. MILLER: Objection. 12 QUESTIONS BY MR. RESTAINO: 13 Q. Let me rephrase. 14 Did you read the entire report 15 versus skimming it? 16 A. Two very different questions. 17 Q. Did you read her entire report? 18 A. No. 19 And now that we've defined in 20 its totality, I can perhaps go back and amend 21 my answers. 22 I generally skim all of these 23 documents. It's extraordinarily difficult 24 and time-consuming to read every word in 25 their totality.</p>
<p style="text-align: right;">Page 31</p> <p>1 Dr. Benjamin Neel in the professional sense? 2 A. Yes. 3 Q. And you read his deposition and 4 their exhibits? 5 A. Yes. 6 Q. And also on number 7 on that 7 list is the expert report. 8 Did you read the expert report 9 of Dr. Benjamin Neel in its totality? 10 MS. MILLER: Objection. 11 THE WITNESS: Yes. 12 QUESTIONS BY MR. RESTAINO: 13 Q. The number 2 on the list is a 14 Cheryl, and the last name is S-a-e-n-z, and 15 I'm not sure how it's pronounced. 16 A. Saenz. 17 Q. Do you know Cheryl Saenz in the 18 sense of walking up to her, shaking her hand, 19 saying "hi"? 20 A. Yes. 21 Q. Okay. And how do you know her? 22 A. I've known her for many years 23 when she was a GYN oncology fellow at the 24 Memorial Sloan Kettering Cancer Center. 25 Well, she and indeed all of the GYN oncology</p>	<p style="text-align: right;">Page 33</p> <p>1 Q. I understand. Thank you. 2 Number 3 on the list is the 3 deposition of Ie-Ming Shih, S-h-i-h. 4 Do you know Dr. Shih? 5 A. Yes. 6 Q. And did you skim his deposition 7 or read every question and every answer? 8 A. I skimmed his -- I'm assuming 9 we're talking about deposition transcript. 10 Yes. 11 Q. Okay. And number 10 is the 12 expert report of Dr. Shih, and same question: 13 Did you read the entire report? 14 A. I skimmed it. 15 Q. Okay. Attached to the report 16 was a study report representative of a 17 histopathological study that Dr. Shih has 18 performed. 19 Did you read that study report 20 also? 21 MS. MILLER: Objection. 22 THE WITNESS: I skimmed it in 23 an unusually cursory fashion. 24 QUESTIONS BY MR. RESTAINO: 25 Q. Did you read -- because I do</p>



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<p style="text-align: right;">Page 34</p> <p>1 not see it on here but within your expert 2 report. 3 You read Dr. Saed's expert 4 report, correct? 5 MS. MILLER: Well, this is the 6 supplemental list, so you wouldn't see 7 it on here. 8 MR. RESTAINO: Yes. 9 MS. MILLER: Do you want to go 10 back to his original materials relied 11 on now? 12 MR. RESTAINO: Don't think we 13 need to. Just want to know if he's 14 read Dr. Saed's report. 15 THE WITNESS: No, we're just 16 using a lot of names. I'm sorry. 17 Dr. Saed, yes, I read his 18 expert report, yes. 19 QUESTIONS BY MR. RESTAINO: 20 Q. And he's had his deposition 21 taken a couple of times, correct? 22 A. I am familiar with two 23 deposition transcripts, two separate 24 documents, which I would infer amounted to 25 two depositions.</p>	<p style="text-align: right;">Page 36</p> <p>1 you refer to the materials considered 2 in your report. 3 Do you have this? Do you want 4 it? 5 THE WITNESS: Sure. 6 MS. MILLER: Do you have the 7 report? 8 Can I give him a copy of the 9 report, or are you going to mark it? 10 MR. RESTAINO: Did I not give 11 him the report yet? 12 MS. MILLER: No. 13 MR. RESTAINO: Then let's do 14 that. 15 MS. MILLER: So... 16 (Boyd Exhibit 5 marked for 17 identification.) 18 QUESTIONS BY MR. RESTAINO: 19 Q. Previously marked as Exhibit 5 20 is a copy of your expert report. 21 MS. MILLER: And this has -- 22 what's attached to this? Because I 23 see you did the CV separately. 24 I'm confused. This also has a 25 CV? Oh, no, this is mine.</p>
<p style="text-align: right;">Page 35</p> <p>1 Q. Understood. Thank you. 2 Doctor, looking at the 3 supplemental materials considered, number 1 4 through 15, including deposition transcripts 5 and expert reports, these are all 6 individuals' deposition transcripts, exhibits 7 and expert reports for experts on behalf of 8 Johnson &amp; Johnson, correct? 9 A. Yes, I believe so. 10 I'm sorry, I still have a 11 little trouble distinguishing the legal 12 representation from the corporation, but, 13 yes. 14 Q. And if at any time you're 15 unsure, then please ask, and the attorneys 16 present will try to straighten it out so that 17 you have a full understanding. 18 Other than Dr. Saed, his 19 deposition testimony and his expert report, 20 have you reviewed any of the expert reports 21 written by any of the other experts on behalf 22 of the plaintiffs? 23 MS. MILLER: I would refer you 24 to the materials considered. You said 25 it wasn't a memory test, so why don't</p>	<p style="text-align: right;">Page 37</p> <p>1 It's just the report. 2 MR. RESTAINO: It is just the 3 report. 4 MS. MILLER: Does it include 5 the materials considered? 6 THE WITNESS: I'm seeing on 7 page 25 materials considered, yeah. 8 MS. MILLER: Go ahead. 9 Is there a question pending, or 10 do you want to ask it again since 11 we -- 12 QUESTIONS BY MR. RESTAINO: 13 Q. I'll ask it again now that they 14 have it in front of you. 15 With this available to refresh 16 your memory, do you recall reading, other 17 than for Dr. Saed, any of the expert reports 18 for the plaintiffs' experts in this regard? 19 A. Vaguely. 20 Q. Okay. So, for example, 21 number 9 is the expert report of Daniel L. 22 Clarke, with an E, hyphen, Pearson. 23 Do you know Dr. Clarke-Pearson? 24 A. We've met. 25 Q. Did you meet when you were at</p>

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<p style="text-align: right;">Page 38</p> <p>1 University of North Carolina?</p> <p>2 A. I never -- well, our employment</p> <p>3 at the University of North Carolina didn't</p> <p>4 overlap, so, no.</p> <p>5 Q. Okay. In fact, you've</p> <p>6 coauthored a paper with Dr. Clarke-Pearson</p> <p>7 titled "Mutation of the P53 Tumor-Suppressor</p> <p>8 Gene is Not a Feature of Endometrial</p> <p>9 Hyperplasias."</p> <p>10 Does that sound familiar?</p> <p>11 A. I'll take your word for it.</p> <p>12 Q. Okay. Dr. Clarke-Pearson is a</p> <p>13 gynecological oncologist; is that your</p> <p>14 understanding?</p> <p>15 A. Until retirement, yes.</p> <p>16 Q. Okay. Well, he's still a</p> <p>17 gynecological oncologist, not practicing,</p> <p>18 correct?</p> <p>19 MS. MILLER: Objection.</p> <p>20 MR. RESTAINO: I'll withdraw</p> <p>21 the question.</p> <p>22 QUESTIONS BY MR. RESTAINO:</p> <p>23 Q. Doctor, are you an expert in</p> <p>24 gynecology?</p> <p>25 MS. MILLER: Objection.</p>	<p style="text-align: right;">Page 40</p> <p>1 the witness, please?</p> <p>2 MS. MILLER: I don't think that</p> <p>3 was coaching the witness.</p> <p>4 MR. RESTAINO: Okay. Well, you</p> <p>5 know what? It really doesn't matter</p> <p>6 what you think; it's what the Federal</p> <p>7 Rules say. The word "objection"</p> <p>8 works.</p> <p>9 THE WITNESS: I'm sorry, could</p> <p>10 you repeat the question?</p> <p>11 QUESTIONS BY MR. RESTAINO:</p> <p>12 Q. Sure.</p> <p>13 For purpose of developing your</p> <p>14 opinions in this litigation, did you not want</p> <p>15 to see what Dr. Clarke-Pearson had to say on</p> <p>16 the matter?</p> <p>17 MS. MILLER: Objection.</p> <p>18 THE WITNESS: I'm sorry, I just</p> <p>19 find that question very convoluted and</p> <p>20 difficult to answer.</p> <p>21 QUESTIONS BY MR. RESTAINO:</p> <p>22 Q. Okay. Do you know if</p> <p>23 Dr. Clarke-Pearson is still practicing?</p> <p>24 A. Well, for the third time, my</p> <p>25 understanding is that he's retired.</p>
<p style="text-align: right;">Page 39</p> <p>1 THE WITNESS: I do not hold</p> <p>2 myself out to be an expert in</p> <p>3 gynecology.</p> <p>4 QUESTIONS BY MR. RESTAINO:</p> <p>5 Q. Do you hold yourself out to be</p> <p>6 an expert in medical oncology?</p> <p>7 MS. MILLER: Objection.</p> <p>8 THE WITNESS: No.</p> <p>9 QUESTIONS BY MR. RESTAINO:</p> <p>10 Q. Dr. Clarke-Pearson is a</p> <p>11 gynecological oncologist, correct?</p> <p>12 A. I would offer the same answer</p> <p>13 that I previously rendered. Before he</p> <p>14 retired, it's my understanding that he was a</p> <p>15 gynecologic oncologist, yes.</p> <p>16 Q. For purposes of developing</p> <p>17 opinions in this litigation, did you not want</p> <p>18 to see what Dr. Clarke-Pearson had to say on</p> <p>19 the matter?</p> <p>20 MS. MILLER: Objection.</p> <p>21 I don't even know what you mean</p> <p>22 by that.</p> <p>23 If you do, you can answer.</p> <p>24 MR. RESTAINO: Jessica, can we</p> <p>25 just say "objection" without coaching</p>	<p style="text-align: right;">Page 41</p> <p>1 Q. Do you know if he's retired as</p> <p>2 the chair while still practicing?</p> <p>3 A. Could you clarify the chair of</p> <p>4 what and practicing what, please?</p> <p>5 Q. Well, do you understand that he</p> <p>6 was the chairman of gynecologic oncology</p> <p>7 there at University of North Carolina?</p> <p>8 A. No, he was not.</p> <p>9 Q. What was his position?</p> <p>10 A. Chair of the department of</p> <p>11 obstetrics and gynecology at the University</p> <p>12 of North Carolina.</p> <p>13 Q. Do you know if he's retired as</p> <p>14 chair of that position?</p> <p>15 A. That's my understanding, yes.</p> <p>16 Q. But do you know if he's stopped</p> <p>17 the practice of medicine?</p> <p>18 A. He never practiced medicine.</p> <p>19 He was a gynecologic oncologist. They're</p> <p>20 typically considered surgeons.</p> <p>21 Q. And in order to be a surgeon,</p> <p>22 one has to be licensed as a medical doctor,</p> <p>23 which by definition entails medicine; is that</p> <p>24 correct?</p> <p>25 MS. MILLER: Objection.</p>

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<p style="text-align: right;">Page 42</p> <p>1 THE WITNESS: The practice of</p> <p>2 surgery is the practice of medicine,</p> <p>3 I'll agree.</p> <p>4 QUESTIONS BY MR. RESTAINO:</p> <p>5 Q. Okay. Now, if you're not an</p> <p>6 expert in gynecology and you're not an expert</p> <p>7 in gynecological oncology, and you know a</p> <p>8 Dr. Clarke-Pearson, who is a gynecological</p> <p>9 oncologist, did you not have any interest in</p> <p>10 ascertaining what his opinions were in this</p> <p>11 litigation regarding talc and ovarian cancer?</p> <p>12 MS. MILLER: Objection.</p> <p>13 This misstates his testimony.</p> <p>14 I mean, this question is extremely</p> <p>15 misleading. I'm sorry, I know you</p> <p>16 don't want me to object --</p> <p>17 MR. RESTAINO: Jessica, let me</p> <p>18 help you. O-b-j-e-c-t-i-o-n. Do you</p> <p>19 need me to write that on a piece of</p> <p>20 paper and put it in front of you?</p> <p>21 MS. MILLER: Do you need me to</p> <p>22 write on a piece of paper how to ask</p> <p>23 fair questions?</p> <p>24 That was not a fair question.</p> <p>25 He told you he read the guy's expert</p>	<p style="text-align: right;">Page 44</p> <p>1 opinions are in this litigation?</p> <p>2 MS. MILLER: Objection.</p> <p>3 THE WITNESS: I respectfully</p> <p>4 request that you not yell at me.</p> <p>5 QUESTIONS BY MR. RESTAINO:</p> <p>6 Q. Doctor, do you know what</p> <p>7 Dr. Clarke-Pearson's objections are in this</p> <p>8 litigation -- his opinions are in this</p> <p>9 litigation?</p> <p>10 A. Not really.</p> <p>11 Q. Do you know Arch Carson, MD,</p> <p>12 Ph.D., physician, toxicologist, out of the</p> <p>13 University of Texas?</p> <p>14 A. I'm sorry, are we reading from</p> <p>15 somewhere?</p> <p>16 Q. My questions.</p> <p>17 A. Something that I have?</p> <p>18 Q. No.</p> <p>19 There's a plaintiff attorney</p> <p>20 {sic} by the name of Arch Carson, MD, Ph.D.</p> <p>21 MS. MILLER: Objection.</p> <p>22 MR. RESTAINO: A physician</p> <p>23 toxicologist.</p> <p>24 MS. MILLER: You said he's an</p> <p>25 attorney. Is he an attorney for you</p>
<p style="text-align: right;">Page 43</p> <p>1 report --</p> <p>2 MR. RESTAINO: The word</p> <p>3 "objection" then covers it --</p> <p>4 MS. MILLER: -- and you keep</p> <p>5 suggesting this --</p> <p>6 MR. RESTAINO: And the judge</p> <p>7 will decide what's fair and what's not</p> <p>8 fair.</p> <p>9 MS. MILLER: Okay.</p> <p>10 MR. RESTAINO: We may have a</p> <p>11 professional disagreement, and you say</p> <p>12 "objection." And I look at it and</p> <p>13 think, okay, let me rephrase it.</p> <p>14 MS. MILLER: You didn't</p> <p>15 rephrase it.</p> <p>16 MR. RESTAINO: Let's not do</p> <p>17 that all day.</p> <p>18 MS. MILLER: You've done it</p> <p>19 three times, the same objectionable</p> <p>20 question, so I don't --</p> <p>21 MR. RESTAINO: Because he's not</p> <p>22 answering it.</p> <p>23 QUESTIONS BY MR. RESTAINO:</p> <p>24 Q. Doctor, do you have any</p> <p>25 interest in what Dr. Clarke-Pearson's</p>	<p style="text-align: right;">Page 45</p> <p>1 guys, too?</p> <p>2 MR. RESTAINO: He's a physician</p> <p>3 toxicologist out of the University of</p> <p>4 Texas, a plaintiff expert.</p> <p>5 QUESTIONS BY MR. RESTAINO:</p> <p>6 Q. Do you know Dr. Carson or know</p> <p>7 of him?</p> <p>8 A. Neither.</p> <p>9 Q. Are you an expert in</p> <p>10 toxicology?</p> <p>11 A. No.</p> <p>12 Q. Did you have any interest in</p> <p>13 seeing what a plaintiff's expert in</p> <p>14 toxicology's opinions were in this</p> <p>15 litigation?</p> <p>16 MS. MILLER: Objection.</p> <p>17 THE WITNESS: I think it's fair</p> <p>18 to say that with an unlimited amount</p> <p>19 of time, I would have had some degree</p> <p>20 of curiosity and interest in reading</p> <p>21 every document associated with this</p> <p>22 litigation.</p> <p>23 But with two full-time jobs, a</p> <p>24 family and the time constraints that</p> <p>25 we're under, I simply have to focus on</p>

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<p style="text-align: right;">Page 46</p> <p>1 what I think is most relevant to my</p> <p>2 role in this litigation, which is</p> <p>3 offering opinions on Dr. Saed's work</p> <p>4 specifically and more generally on</p> <p>5 biological plausibility of the</p> <p>6 relationship of the -- the</p> <p>7 hypothesized association of perineal</p> <p>8 use of talc and ovarian cancer.</p> <p>9 QUESTIONS BY MR. RESTAINO:</p> <p>10 Q. And I appreciate, understand</p> <p>11 time constraints we all function under, but</p> <p>12 under the supplemental materials considered</p> <p>13 list, there are 15 documents, including</p> <p>14 deposition and exhibits and expert reports of</p> <p>15 multiple defense experts.</p> <p>16 You had the time to read those</p> <p>17 but not the plaintiff expert reports; is that</p> <p>18 true?</p> <p>19 MS. MILLER: Objection.</p> <p>20 Mischaracterizes his testimony.</p> <p>21 THE WITNESS: I believe it's</p> <p>22 fair to say I had time to at the very</p> <p>23 least cursorily skim all of the</p> <p>24 materials considered to one degree or</p> <p>25 another.</p>	<p style="text-align: right;">Page 48</p> <p>1 QUESTIONS BY MR. RESTAINO:</p> <p>2 Q. Okay. Do you know or have you</p> <p>3 heard of Dr. Jack Siemiatycki,</p> <p>4 S-i-e-m-i-a-t-y-c-k-i?</p> <p>5 A. I don't know the doctor.</p> <p>6 Q. Okay. Did you review any</p> <p>7 epidemiological report written by any of the</p> <p>8 plaintiffs' epidemiological experts?</p> <p>9 A. I don't recall.</p> <p>10 Q. Do you know or know of</p> <p>11 Dr. Judith Wolf, MD, a gynecological</p> <p>12 oncologist with the National Ovarian Cancer</p> <p>13 Coalition?</p> <p>14 A. I'm sorry, that's a complicated</p> <p>15 question. The National Ovarian Cancer</p> <p>16 Coalition is a foundation.</p> <p>17 I know of Dr. Judith Wolf. To</p> <p>18 the best of my ability to recall, she, at</p> <p>19 least at some point in her career, has worked</p> <p>20 as a gynecologic oncologist at the MD</p> <p>21 Anderson Cancer Center.</p> <p>22 Q. Have you ever coauthored any</p> <p>23 publications with Dr. Wolf?</p> <p>24 A. I cannot say with certainty.</p> <p>25 I've coauthored lots of papers with lots of</p>
<p style="text-align: right;">Page 47</p> <p>1 QUESTIONS BY MR. RESTAINO:</p> <p>2 Q. Did you skim the expert report</p> <p>3 of Ellen Blair Smith, a physician,</p> <p>4 gynecologist, oncologist?</p> <p>5 A. I don't remember doing so.</p> <p>6 Q. Okay. Do you recall -- or do</p> <p>7 you know Ellen Blair Smith, Dr. Smith?</p> <p>8 A. No.</p> <p>9 Q. In 2017, did you coauthor a</p> <p>10 paper titled "Multi-Disciplinary Summit on</p> <p>11 Genetic Services for Women with Gynecological</p> <p>12 Cancers: A Society of Gynecologic Oncology</p> <p>13 White Paper"?</p> <p>14 Do you recall that publication?</p> <p>15 A. I do.</p> <p>16 Q. And do you recall Dr. Smith</p> <p>17 being a coauthor with you on that paper?</p> <p>18 A. No.</p> <p>19 Q. Do you know that Dr. Smith is a</p> <p>20 gynecological oncologist?</p> <p>21 MS. MILLER: Objection.</p> <p>22 He said he doesn't know who she</p> <p>23 is.</p> <p>24 THE WITNESS: I don't know who</p> <p>25 she is.</p>	<p style="text-align: right;">Page 49</p> <p>1 coauthors, and some I remember, and some I</p> <p>2 don't.</p> <p>3 Q. I understand.</p> <p>4 Dr. Judith Zelikoff,</p> <p>5 Z-e-l-i-c-o-f-f, is a professor of at NYU.</p> <p>6 Do you know Dr. Zelikoff?</p> <p>7 A. No.</p> <p>8 Q. And Dr. Laura Plunkett, Ph.D.,</p> <p>9 is a pharmacologist, toxicologist.</p> <p>10 Do you know Dr. Plunkett?</p> <p>11 A. No.</p> <p>12 Q. Are you an expert in</p> <p>13 pharmacology?</p> <p>14 MS. MILLER: Objection.</p> <p>15 THE WITNESS: No.</p> <p>16 QUESTIONS BY MR. RESTAINO:</p> <p>17 Q. Did you have any interest in</p> <p>18 seeing what plaintiff expert pharmacologist</p> <p>19 opinions were regarding talc and ovarian</p> <p>20 cancer?</p> <p>21 MS. MILLER: Objection.</p> <p>22 THE WITNESS: Again, that's a</p> <p>23 very difficult question to answer.</p> <p>24 I'm interested in many things.</p> <p>25</p>

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<p style="text-align: right;">Page 50</p> <p>1 QUESTIONS BY MR. RESTAINO: 2 Q. Did you not have the interest, 3 though, to pick up her expert report and read 4 it? 5 MS. MILLER: Objection. 6 THE WITNESS: I think interest 7 and time are two different things. 8 QUESTIONS BY MR. RESTAINO: 9 Q. Sarah Kane, MD, is a 10 pathologist up in the Boston area. 11 Do you know of Dr. Kane? 12 A. I've seen her name. 13 Q. And do you recall where you've 14 seen her name? 15 A. In some of the deposition 16 transcripts associated with this litigation. 17 Q. And did you read Dr. Kane's 18 report as an expert in pathology? 19 A. I skimmed it. 20 Q. Are you an expert in pathology? 21 A. No. 22 Q. Do you know Shawn Levy, 23 L-e-v-y, Ph.D., with the Genomics Services 24 Laboratory at the Hudson Alpha Institute for 25 Biotechnology?</p>	<p style="text-align: right;">Page 52</p> <p>1 QUESTIONS BY MR. RESTAINO: 2 Q. Do you know how many 3 publications on ovarian cancer Dr. Cramer has 4 in the peer-reviewed literature? 5 A. I'm sure I don't. 6 Q. Okay. Did you have any 7 interest in seeing what Dr. Cramer had to say 8 in the -- this litigation? 9 MS. MILLER: Objection. 10 THE WITNESS: I think it's fair 11 to say that I'm relatively familiar 12 with Dr. Cramer's work over the years. 13 I cannot say that I devoted a 14 substantial amount of time to 15 reviewing his opinion in this 16 particular context over the past 17 several months. 18 QUESTIONS BY MR. RESTAINO: 19 Q. Would you consider yourself an 20 expert in the epidemiology of ovarian cancer 21 and its associated risk factors? 22 MS. MILLER: Objection. 23 THE WITNESS: Again, a 24 difficult question to answer. I would 25 not consider myself an expert. I</p>
<p style="text-align: right;">Page 51</p> <p>1 A. No. 2 Q. And how about Sonal Singh, 3 S-i-n-g, {sic} MD, MPH, a medical 4 epidemiologist? 5 A. A medical epidemiologist? No. 6 Q. Daniel Cramer, MD, DSC, at 7 Brigham and Women's Hospital, also a 8 physician and epidemiologist. 9 Do you know Dan Cramer? 10 A. Yes. 11 Q. Do you know him to be a 12 professor of epidemiology at the Harvard 13 T.H. Chan School of Public Health? 14 A. I honestly can't say what his 15 current position is. 16 Q. Okay. Are you aware of 17 Dr. Cramer's work and publications pertaining 18 to ovarian cancer? 19 MS. MILLER: Objection. 20 THE WITNESS: I'm aware that 21 Dr. Cramer over many years has had an 22 interest, a research interest, in the 23 issue of an association with talc 24 exposure and the development of 25 ovarian cancer.</p>	<p style="text-align: right;">Page 53</p> <p>1 would say that I'm familiar with some 2 of the basic concepts of epidemiologic 3 aspects of ovarian cancer. 4 QUESTIONS BY MR. RESTAINO: 5 Q. Okay. If there were instances 6 regarding the epidemiological principles 7 associated with studies of ovarian cancer and 8 talc, would you defer to someone like Dan 9 Cramer as a medical epidemiologist? 10 MS. MILLER: Objection. 11 THE WITNESS: Defer in what 12 context? 13 QUESTIONS BY MR. RESTAINO: 14 Q. If you're not understanding 15 what the epidemiological principles may be, 16 would you defer to an epidemiologist? 17 MS. MILLER: Objection. 18 THE WITNESS: So your first 19 question was would I defer to 20 Dr. Cramer, and your second question 21 was to an epidemiologist? 22 QUESTIONS BY MR. RESTAINO: 23 Q. Yes. 24 A. Which one am I answering, 25 please?</p>

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<p style="text-align: right;">Page 54</p> <p>1 MS. MILLER: Well, they also</p> <p>2 had different "ifs," so...</p> <p>3 QUESTIONS BY MR. RESTAINO:</p> <p>4 Q. If you're not understanding</p> <p>5 what the epidemiological principles may be,</p> <p>6 would you defer to an epidemiologist?</p> <p>7 MS. MILLER: Objection.</p> <p>8 Mischaracterizes his testimony.</p> <p>9 THE WITNESS: I might defer to</p> <p>10 anyone on any given day about any</p> <p>11 given topic that had to do with a</p> <p>12 field of inquiry in which I'm not an</p> <p>13 expert.</p> <p>14 QUESTIONS BY MR. RESTAINO:</p> <p>15 Q. Okay. Are you an expert in the</p> <p>16 epidemiological principle of effect</p> <p>17 modification?</p> <p>18 A. No.</p> <p>19 Q. As such, would you defer to a</p> <p>20 medical epidemiologist such as Dan Cramer to</p> <p>21 explain effect modification and whatever role</p> <p>22 it may have regarding talcum powder and</p> <p>23 ovarian cancer?</p> <p>24 MS. MILLER: Objection.</p> <p>25 THE WITNESS: If I was indeed</p>	<p style="text-align: right;">Page 56</p> <p>1 Q. Okay. And who was that?</p> <p>2 A. Ms. Miller.</p> <p>3 Q. And have you talked with --</p> <p>4 worked with Ms. Miller in the past?</p> <p>5 A. Prior to mid-December of 2018?</p> <p>6 Q. Yes, sir.</p> <p>7 A. No.</p> <p>8 Q. Prior to your meeting with</p> <p>9 Ms. Miller, had you conducted any original</p> <p>10 research on your part to the association, if</p> <p>11 any, between talcum powder and the</p> <p>12 development of ovarian cancer?</p> <p>13 MS. MILLER: Objection.</p> <p>14 THE WITNESS: No.</p> <p>15 QUESTIONS BY MR. RESTAINO:</p> <p>16 Q. Prior to you meeting with</p> <p>17 Ms. Miller in December of 2018, had you</p> <p>18 lectured to any professional society -- and</p> <p>19 by that I mean medical and/or scientific --</p> <p>20 regarding the association between talcum</p> <p>21 powder and ovarian cancer?</p> <p>22 A. No.</p> <p>23 Q. Prior to your meeting with</p> <p>24 Ms. Miller in December of 2018, had you</p> <p>25 formulated an opinion regarding an</p>
<p style="text-align: right;">Page 55</p> <p>1 interested in an acute sense about</p> <p>2 that particular issue, I would</p> <p>3 probably approach someone that I knew</p> <p>4 better than Dr. Cramer and certainly</p> <p>5 perhaps closer to home.</p> <p>6 QUESTIONS BY MR. RESTAINO:</p> <p>7 Q. Okay. When were you first</p> <p>8 contacted by any representative of Johnson &amp;</p> <p>9 Johnson to serve as an expert in this</p> <p>10 litigation?</p> <p>11 A. Could you repeat the question,</p> <p>12 please?</p> <p>13 Q. When you were first contacted</p> <p>14 by any representative of Johnson &amp; Johnson to</p> <p>15 see if you would work as an expert witness in</p> <p>16 this litigation?</p> <p>17 MS. MILLER: Objection.</p> <p>18 THE WITNESS: To my knowledge,</p> <p>19 I've never been approached by a</p> <p>20 representative of Johnson &amp; Johnson.</p> <p>21 QUESTIONS BY MR. RESTAINO:</p> <p>22 Q. Were you ever -- when were you</p> <p>23 approached by any attorney representing</p> <p>24 Johnson &amp; Johnson?</p> <p>25 A. Mid-December of 2018.</p>	<p style="text-align: right;">Page 57</p> <p>1 association between talcum powder and ovarian</p> <p>2 cancer?</p> <p>3 A. Yes.</p> <p>4 Q. And when did you develop that</p> <p>5 opinion?</p> <p>6 A. Over several decades.</p> <p>7 Q. Going back to the 1990s or</p> <p>8 early 2000s?</p> <p>9 A. Hard to say, but I would</p> <p>10 estimate that I may have been aware of</p> <p>11 studies involving a possible association of</p> <p>12 talc exposure and ovarian cancer as long ago</p> <p>13 as the late '80s, early '90s, were such</p> <p>14 studies to have existed.</p> <p>15 Q. Okay. Prior to your meeting</p> <p>16 with Ms. Miller in December of 2018, had you</p> <p>17 formulated an opinion regarding risk factors</p> <p>18 associated with the development of ovarian</p> <p>19 cancer?</p> <p>20 MS. MILLER: I'm going to have</p> <p>21 to keep objecting to these questions.</p> <p>22 He said he was contacted in</p> <p>23 December 2018. He never said he met</p> <p>24 with Ms. Miller in December of 2018,</p> <p>25 and you've now embedded that into like</p>

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<p style="text-align: right;">Page 58</p> <p>1 three questions. 2 And I'm sorry if this is a 3 speaking objection, but that's just 4 not an accurate recitation of his 5 testimony. 6 MR. RESTAINO: Let me withdraw 7 the question. 8 QUESTIONS BY MR. RESTAINO: 9 Q. And relating back to the other 10 questions I asked you, did you, in December 11 of 2018, meet with Jessica Miller or talk 12 with her on the phone? 13 A. My memory is that our first 14 communication was e-mail. 15 Q. And -- 16 A. Subsequent communication was 17 telephone. 18 Q. Okay. So that would apply to 19 all your prior answers when I asked you 20 regarding meeting Ms. Miller? 21 A. I honestly don't remember the 22 questions and how meeting Ms. Miller had been 23 embedded in them. 24 Q. Okay. Prior to any 25 communication with any attorney representing</p>	<p style="text-align: right;">Page 60</p> <p>1 Q. Yes. 2 A. A clinical cancer geneticist 3 and a molecular diagnostician. 4 Q. And what do you mean when you 5 say "a clinical cancer geneticist"? 6 A. Well, cancer genetics, 7 clinical, the clinical implications of cancer 8 genetics, and the -- and the practice of 9 dealing with patients with genetic 10 predisposition to cancer, as well as a 11 clinical molecular diagnostics practice 12 wherein we examine the genetic architecture 13 of an individual patient's tumor in order to 14 perform precision cancer therapy. 15 Q. Okay. You're not a medical 16 doctor; is that correct? 17 A. That's correct. 18 Q. When you were studying either 19 undergrad or for your Ph.D., did you take 20 general anatomy? 21 A. Probably. 22 Q. Did you dissect a cadaver? 23 A. Human? 24 Q. Yes. 25 A. No.</p>
<p style="text-align: right;">Page 59</p> <p>1 Johnson &amp; Johnson prior to January 1st of 2 2019, you had formulated an opinion regarding 3 talcum powder and ovarian cancer; is that 4 correct? 5 A. That's fair, yes. 6 Q. And what was the basis for that 7 opinion or opinions, if you recall? 8 A. Several decades of a rather 9 passive reading of the literature in general, 10 which given an interest in ovarian cancer is 11 quite typical in my scientists and 12 clinicians. I try to stay abreast of the 13 literature in all forms. 14 Q. Okay. Now, you received your 15 Ph.D. from North Carolina State University; 16 is that correct? 17 A. Yes. 18 Q. Would you describe yourself as 19 a cellular biologist? 20 A. No. 21 Q. How would you introduce 22 yourself to a fellow scientist or physician 23 at a meeting you first -- meet for the first 24 time? 25 A. Today?</p>	<p style="text-align: right;">Page 61</p> <p>1 Q. Have you ever studied through 2 dissection, textbook or virtual reality the 3 anatomy of the female genitourinary tract? 4 A. I would refer to it as the 5 female reproductive tract, but I think the 6 answer to your question is yes. 7 MR. RESTAINO: Okay. 8 MS. MILLER: Is this a good 9 time for break? We've been going an 10 hour. 11 MR. RESTAINO: Sure. 12 VIDEOGRAPHER: Off the record 13 at 10:02 a.m. 14 (Off the record at 10:02 a.m.) 15 VIDEOGRAPHER: We're back on 16 record at 10:14 a.m. 17 QUESTIONS BY MR. RESTAINO: 18 Q. Welcome back, Doctor. 19 A. Thank you. 20 Q. During the course of today 21 there are going to be some documents that 22 we'll refer to frequently. Your expert 23 report, that one you might want to keep, you 24 know, in one particular pile. And some of 25 the others, like CV and maybe an article that</p>

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<p style="text-align: right;">Page 62</p> <p>1 we just look at momentarily, I'll let you</p> <p>2 know, and you can just get it out of your</p> <p>3 way, if that helps.</p> <p>4 A. Excellent, thank you.</p> <p>5 Q. Now, we had discussed that</p> <p>6 prior to your communication of any sort with</p> <p>7 Ms. Miller, that you had some opinions</p> <p>8 regarding talc and ovarian cancer; is that</p> <p>9 correct?</p> <p>10 A. Yes.</p> <p>11 Q. As you sit here today, can you</p> <p>12 tell us what those opinions were?</p> <p>13 A. My opinion, generally speaking,</p> <p>14 was that the existing body of scientific</p> <p>15 evidence did not support a causal association</p> <p>16 between perineal talc exposure and the</p> <p>17 development of epithelial ovarian carcinoma.</p> <p>18 And, of course, we're speaking</p> <p>19 about many distinct diseases when we refer to</p> <p>20 EOC, but...</p> <p>21 Q. Did you have, at the time you</p> <p>22 held an opinion that the existing body of</p> <p>23 scientific evidence did not support a causal</p> <p>24 association, an opinion regarding the</p> <p>25 biologically plausible risk factors for</p>	<p style="text-align: right;">Page 64</p> <p>1 of the term is any factor, behavior,</p> <p>2 exposure, habit of lifestyle that</p> <p>3 either increases or decreases in a</p> <p>4 substantive fashion one's risk for</p> <p>5 ovarian cancer.</p> <p>6 QUESTIONS BY MR. RESTAINO:</p> <p>7 Q. Okay. Before we broke, I was</p> <p>8 asking if you had taken a general anatomy</p> <p>9 course or class regarding not only general</p> <p>10 anatomy but also the female reproductive</p> <p>11 tract, correct?</p> <p>12 Do you recall those questions?</p> <p>13 A. You're correct that I recall</p> <p>14 those questions.</p> <p>15 Q. Okay. As you sit here today,</p> <p>16 do you know what a woman's labia are,</p> <p>17 anatomically speaking?</p> <p>18 A. Are you referring to the</p> <p>19 components of the vulva?</p> <p>20 Q. To however you would define a</p> <p>21 woman's labia.</p> <p>22 A. The labia majoras and labia</p> <p>23 minoras I would consider components of the</p> <p>24 external female genitalia, typically referred</p> <p>25 to in aggregate as the vulva.</p>
<p style="text-align: right;">Page 63</p> <p>1 ovarian cancer?</p> <p>2 MS. MILLER: Objection.</p> <p>3 THE WITNESS: I'm sorry, but I</p> <p>4 just can't follow that question.</p> <p>5 QUESTIONS BY MR. RESTAINO:</p> <p>6 Q. Did you --</p> <p>7 A. Maybe break it down.</p> <p>8 Q. Yes.</p> <p>9 Did you have an opinion, prior</p> <p>10 to January 1, 2019, regarding biologically</p> <p>11 plausible risk factors for the development of</p> <p>12 ovarian cancer?</p> <p>13 A. Oh, I'm sorry, yes.</p> <p>14 Q. Okay. Can you define for us as</p> <p>15 we go forward in the day your definition of a</p> <p>16 risk factor?</p> <p>17 A. I missed a couple words there</p> <p>18 in the middle of that question.</p> <p>19 Q. Just going forward for the</p> <p>20 course of the day, I want to use your</p> <p>21 definition. So can you define for us your</p> <p>22 definition of a risk factor, specifically as</p> <p>23 it relates to ovarian cancer?</p> <p>24 MS. MILLER: Objection.</p> <p>25 THE WITNESS: My understanding</p>	<p style="text-align: right;">Page 65</p> <p>1 Q. Okay. And collectively as the</p> <p>2 vulva, do you have an opinion as to whether</p> <p>3 the vulva exists as a barrier between the</p> <p>4 external environment and the vagina?</p> <p>5 MS. MILLER: Objection.</p> <p>6 THE WITNESS: I'm not prepared</p> <p>7 to testify about anatomical barriers</p> <p>8 between the environment and anything</p> <p>9 else.</p> <p>10 QUESTIONS BY MR. RESTAINO:</p> <p>11 Q. Okay. Would you defer to a</p> <p>12 gynecologist or a physician in that regard?</p> <p>13 MS. MILLER: Objection.</p> <p>14 THE WITNESS: If I was</p> <p>15 interested in pursuing such a</p> <p>16 question, it's much more likely that I</p> <p>17 would start pulling out textbooks and</p> <p>18 scientific papers on the topic.</p> <p>19 QUESTIONS BY MR. RESTAINO:</p> <p>20 Q. Okay. As you sit here today,</p> <p>21 do you have an opinion as to whether the</p> <p>22 vulva, as defined by yourself, closes off the</p> <p>23 vagina from the external environment?</p> <p>24 A. Again --</p> <p>25 MS. MILLER: Objection. Asked</p>

17 (Pages 62 to 65)

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<p style="text-align: right;">Page 66</p> <p>1 and answered.</p> <p>2 Please give me a second to</p> <p>3 object, even though my objections --</p> <p>4 thank you.</p> <p>5 THE WITNESS: Again, I'm not</p> <p>6 prepared to offer an opinion on that</p> <p>7 topic.</p> <p>8 QUESTIONS BY MR. RESTAINO:</p> <p>9 Q. Have you ever diagnosed a woman</p> <p>10 with ovarian cancer?</p> <p>11 A. No.</p> <p>12 Q. And as a Ph.D. scientist, is it</p> <p>13 correct in saying that you do not have the --</p> <p>14 you don't have the privileges to treat women</p> <p>15 with cancer?</p> <p>16 MS. MILLER: Objection.</p> <p>17 THE WITNESS: That's a</p> <p>18 complicated question.</p> <p>19 I oversee a clinical, which is</p> <p>20 to say CLIA-certified and</p> <p>21 CAP-accredited, molecular diagnostics</p> <p>22 laboratory wherein we subject ovarian</p> <p>23 cancers, tumor tissues themselves, to</p> <p>24 a rather complex next generation</p> <p>25 sequencing-based interrogation of the</p>	<p style="text-align: right;">Page 68</p> <p>1 opposed to traditional chemotherapy agents.</p> <p>2 But to the extent that anything is prescribed</p> <p>3 to the patient, that would be the oncologist,</p> <p>4 correct.</p> <p>5 Q. Same answer if I was to ask you</p> <p>6 if you were licensed to perform surgery on a</p> <p>7 woman?</p> <p>8 A. I'm not an MD.</p> <p>9 Q. Will you be offering any</p> <p>10 opinions regarding strengths and/or</p> <p>11 weaknesses of any of the epidemiological</p> <p>12 studies looking at the association between</p> <p>13 talcum powder and ovarian cancer?</p> <p>14 MS. MILLER: I just want to</p> <p>15 look at that question.</p> <p>16 Objection.</p> <p>17 THE WITNESS: I was asked to</p> <p>18 render opinions here today on the</p> <p>19 veracity of Dr. Saed's work, his</p> <p>20 testimony, his expert report</p> <p>21 specifically, and generally perhaps on</p> <p>22 biological plausibility, getting us</p> <p>23 from association to causality in this</p> <p>24 particular litigation.</p> <p>25 MR. RESTAINO: And this is one</p>
<p style="text-align: right;">Page 67</p> <p>1 genomic architecture of aforementioned</p> <p>2 tumor in an attempt to link specific</p> <p>3 genetic mutations in that tumor to</p> <p>4 specific precision therapeutics.</p> <p>5 And the end result of that</p> <p>6 clinical laboratory process is the</p> <p>7 generation of what's known as</p> <p>8 molecular pathology report, which is</p> <p>9 then returned to the ordering</p> <p>10 oncologist, which allows he or she to</p> <p>11 make a hopefully precision therapeutic</p> <p>12 treatment determination.</p> <p>13 QUESTIONS BY MR. RESTAINO:</p> <p>14 Q. And if that -- was there a</p> <p>15 period?</p> <p>16 A. Yes.</p> <p>17 Q. Okay. And if the organized</p> <p>18 oncologist decides to prescribe a specific</p> <p>19 regimen of chemotherapy, he or she would be</p> <p>20 licensed to do that and not yourself; is that</p> <p>21 correct?</p> <p>22 A. Well, let's back up a little</p> <p>23 bit. Actually we were talking about</p> <p>24 precision therapeutics, which typically are</p> <p>25 small molecules or monoclonal antibodies as</p>	<p style="text-align: right;">Page 69</p> <p>1 of those times when I'll say move to</p> <p>2 strike as unresponsive.</p> <p>3 QUESTIONS BY MR. RESTAINO:</p> <p>4 Q. And the question is: Will you</p> <p>5 be offering any opinions regarding strengths</p> <p>6 and/or weaknesses of any of the</p> <p>7 epidemiological studies looking at the</p> <p>8 association between talcum powder and the</p> <p>9 development of ovarian cancer?</p> <p>10 MS. MILLER: Objection.</p> <p>11 THE WITNESS: I will not</p> <p>12 voluntarily be offering any opinions.</p> <p>13 I will do my best to answer any</p> <p>14 question you ask me. Some of them --</p> <p>15 many of them, perhaps, may be that I'm</p> <p>16 not comfortable or qualified to answer</p> <p>17 that question.</p> <p>18 Some I may answer.</p> <p>19 QUESTIONS BY MR. RESTAINO:</p> <p>20 Q. Okay. Do you consider yourself</p> <p>21 an expert in mineralogy?</p> <p>22 A. No.</p> <p>23 Q. And an expert in geology?</p> <p>24 A. No.</p> <p>25 Q. Do you consider yourself an</p>

18 (Pages 66 to 69)

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<p>1 expert in talcum powder?</p> <p>2 MS. MILLER: Objection.</p> <p>3 THE WITNESS: I can honestly</p> <p>4 say I've never met an expert in talcum</p> <p>5 powder.</p> <p>6 QUESTIONS BY MR. RESTAINO:</p> <p>7 Q. Do you have a basic</p> <p>8 understanding of what talcum powder is?</p> <p>9 A. Yes.</p> <p>10 Q. And what is that understanding?</p> <p>11 A. Finely ground talc.</p> <p>12 Q. Would you agree that it is a</p> <p>13 mineral composed of various elements?</p> <p>14 MS. MILLER: Objection.</p> <p>15 THE WITNESS: Could you restate</p> <p>16 the question?</p> <p>17 QUESTIONS BY MR. RESTAINO:</p> <p>18 Q. Would you agree that it is a</p> <p>19 mineral composed of various elements?</p> <p>20 A. What is "it"?</p> <p>21 Q. Talcum powder.</p> <p>22 A. Well, to the extent that talcum</p> <p>23 powder is finely ground talc, I would agree</p> <p>24 that talc is a mineral composed, as all</p> <p>25 minerals are, of particular molecules.</p>	<p>1 40 years to the last time I looked at a</p> <p>2 periodic table. Perhaps silicon.</p> <p>3 Q. Can you explain to us what a</p> <p>4 ligand is, l-i-g-a-n-d?</p> <p>5 A. In my mind, a ligand is any</p> <p>6 substance or molecule that interacts with a</p> <p>7 receptor in a very general sense.</p> <p>8 Q. Do you find ligands attached to</p> <p>9 other compounds? For example, metals?</p> <p>10 MS. MILLER: Objection.</p> <p>11 THE WITNESS: That's such an</p> <p>12 extraordinarily general question, I</p> <p>13 just...</p> <p>14 QUESTIONS BY MR. RESTAINO:</p> <p>15 Q. Let me rephrase it then.</p> <p>16 Are you aware of any ligands</p> <p>17 that by themselves are injected into the</p> <p>18 human body for whatever reason?</p> <p>19 MS. MILLER: Objection.</p> <p>20 THE WITNESS: Again, just -- I</p> <p>21 can't even begin to answer that</p> <p>22 question. It's overly broad.</p> <p>23 QUESTIONS BY MR. RESTAINO:</p> <p>24 Q. What purpose does a ligand</p> <p>25 have, chemically speaking?</p>
Page 71	Page 73
<p>1 Q. Magnesium?</p> <p>2 A. That's one.</p> <p>3 Q. Silicon?</p> <p>4 A. That's another.</p> <p>5 Q. Oxygen?</p> <p>6 A. That's another.</p> <p>7 Q. Hydrogen?</p> <p>8 A. Those are them.</p> <p>9 Q. Would you agree that talc is</p> <p>10 not a mineral -- excuse me, is not a metal?</p> <p>11 A. With all due respect, that's a</p> <p>12 trick question.</p> <p>13 Q. How so?</p> <p>14 MS. MILLER: Objection.</p> <p>15 QUESTIONS BY MR. RESTAINO:</p> <p>16 Q. How can I make the question any</p> <p>17 easier for you without trying to be --</p> <p>18 without any component of tricking?</p> <p>19 A. Talc, as we just discussed,</p> <p>20 consists of multiple elements. One or more</p> <p>21 of those elements from a chemical</p> <p>22 perspective, for example, if one examined the</p> <p>23 periodic table, may be considered a metal.</p> <p>24 Q. Which one?</p> <p>25 A. And I'm thinking now back</p>	<p>1 MS. MILLER: Objection.</p> <p>2 THE WITNESS: Ligands don't</p> <p>3 have purposes.</p> <p>4 QUESTIONS BY MR. RESTAINO:</p> <p>5 Q. They don't?</p> <p>6 MS. MILLER: Is that a</p> <p>7 question?</p> <p>8 MR. RESTAINO: That's a</p> <p>9 question: They don't?</p> <p>10 MS. MILLER: Okay. I'm</p> <p>11 objecting to that then.</p> <p>12 THE WITNESS: I -- you know, I</p> <p>13 hesitate to delve into a debate</p> <p>14 involving syntax or metaphysical</p> <p>15 arguments, but I think humans have a</p> <p>16 purpose generally. I think inert</p> <p>17 compounds are elements.</p> <p>18 QUESTIONS BY MR. RESTAINO:</p> <p>19 Q. I'm sorry, was that a period?</p> <p>20 A. No.</p> <p>21 Q. Oh, okay.</p> <p>22 A. Generally don't have a purpose</p> <p>23 in terms of cognitive function.</p> <p>24 Q. Going back to the periodic</p> <p>25 table, are you familiar with the element</p>

19 (Pages 70 to 73)

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<p style="text-align: right;">Page 74</p> <p>1 gadolinium?</p> <p>2 MS. MILLER: Objection.</p> <p>3 Is this a chemistry class?</p> <p>4 MS. SHARKO: Wrong litigation,</p> <p>5 John.</p> <p>6 MS. MILLER: I know. Yeah.</p> <p>7 It's the wrong litigation; it's the</p> <p>8 wrong expert.</p> <p>9 Is he here as a chemistry</p> <p>10 expert? Because I don't see that</p> <p>11 anywhere in his report.</p> <p>12 QUESTIONS BY MR. RESTAINO:</p> <p>13 Q. Doctor, are you familiar with</p> <p>14 the element gadolinium?</p> <p>15 A. I do not hold myself out as a</p> <p>16 chemist, a mineralogist, a geologist.</p> <p>17 Q. As a scientist, do you know if</p> <p>18 gadolinium had been injected into the human</p> <p>19 body without a ligand around it?</p> <p>20 A. I'm sure it can. I...</p> <p>21 Q. Do you have a basic --</p> <p>22 MS. MILLER: He's like in the</p> <p>23 middle of forming a word, and you're</p> <p>24 interrupting him.</p> <p>25 MR. RESTAINO: Oh, I'm sorry, I</p>	<p style="text-align: right;">Page 76</p> <p>1 any Johnson &amp; Johnson talcum powder product?</p> <p>2 A. Could you please repeat the</p> <p>3 question?</p> <p>4 Q. Do you have an opinion as to</p> <p>5 whether or not there is asbestos present in</p> <p>6 any Johnson &amp; Johnson talcum powder product?</p> <p>7 A. No.</p> <p>8 Q. Do you have an opinion as to</p> <p>9 whether or not there is any fibrous talc</p> <p>10 present in any Johnson &amp; Johnson talcum</p> <p>11 powder?</p> <p>12 A. Again, if we're referring to</p> <p>13 Johnson's baby powder, the answer would be</p> <p>14 no.</p> <p>15 Q. Do you know if there are any</p> <p>16 other suspected carcinogens known to be</p> <p>17 within the fragrant chemicals that can be</p> <p>18 found in Johnson &amp; Johnson baby powder --</p> <p>19 MS. MILLER: Objection.</p> <p>20 QUESTIONS BY MR. RESTAINO:</p> <p>21 Q. -- or talcum powder?</p> <p>22 MS. MILLER: Objection.</p> <p>23 THE WITNESS: I have no</p> <p>24 opinion.</p> <p>25</p>
<p style="text-align: right;">Page 75</p> <p>1 heard a period there.</p> <p>2 MS. MILLER: His mouth was</p> <p>3 open.</p> <p>4 THE WITNESS: I think</p> <p>5 theoretically it's possible to inject</p> <p>6 anything into the human body.</p> <p>7 QUESTIONS BY MR. RESTAINO:</p> <p>8 Q. Okay. Is it safe to inject</p> <p>9 gadolinium without a ligand into the human</p> <p>10 body?</p> <p>11 MS. MILLER: Objection.</p> <p>12 THE WITNESS: I can't answer</p> <p>13 that.</p> <p>14 QUESTIONS BY MR. RESTAINO:</p> <p>15 Q. Do you have a basic</p> <p>16 understanding of what asbestos is?</p> <p>17 A. I have a very basic</p> <p>18 understanding, yes. Not a detailed</p> <p>19 understanding as, again, I'm neither a</p> <p>20 mineralogist nor a geologist nor a chemist.</p> <p>21 Q. Have you ever studied the</p> <p>22 effect of asbestos in the human body?</p> <p>23 A. No.</p> <p>24 Q. Do you have an opinion as to</p> <p>25 whether or not there's asbestos present in</p>	<p style="text-align: right;">Page 77</p> <p>1 QUESTIONS BY MR. RESTAINO:</p> <p>2 Q. Were you ever asked to look</p> <p>3 into whether or not these substances may be</p> <p>4 in Johnson &amp; Johnson talcum powder?</p> <p>5 MS. MILLER: Objection.</p> <p>6 THE WITNESS: No.</p> <p>7 QUESTIONS BY MR. RESTAINO:</p> <p>8 Q. Were you ever asked to look</p> <p>9 into whether or not there are any heavy</p> <p>10 metals present in Johnson &amp; Johnson's talcum</p> <p>11 powder?</p> <p>12 A. No.</p> <p>13 Q. Did you ask to see if Johnson &amp;</p> <p>14 Johnson had any existing data regarding the</p> <p>15 presence of any of these compounds in their</p> <p>16 talcum powder?</p> <p>17 A. Again, a complicated question.</p> <p>18 Asked who?</p> <p>19 Q. Did you ask to see any</p> <p>20 representative of Johnson &amp; Johnson as to</p> <p>21 whether or not there was asbestos in their</p> <p>22 talcum powder?</p> <p>23 MS. MILLER: Objection.</p> <p>24 THE WITNESS: That sentence</p> <p>25 doesn't make sense.</p>

20 (Pages 74 to 77)



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<p style="text-align: right;">Page 78</p> <p>1 MS. MILLER: Yeah.</p> <p>2 THE WITNESS: I've never asked</p> <p>3 to see a representative of Johnson &amp;</p> <p>4 Johnson.</p> <p>5 QUESTIONS BY MR. RESTAINO:</p> <p>6 Q. Did you ever ask to see any</p> <p>7 documentation that Johnson &amp; Johnson may have</p> <p>8 regarding the presence of asbestos in their</p> <p>9 talcum powder?</p> <p>10 MS. MILLER: Objection.</p> <p>11 THE WITNESS: No.</p> <p>12 QUESTIONS BY MR. RESTAINO:</p> <p>13 Q. If there were asbestos in</p> <p>14 Johnson &amp; Johnson's talcum powder, would that</p> <p>15 change any of your opinions that you had</p> <p>16 formulated within your expert report?</p> <p>17 A. My opinions are based on</p> <p>18 Johnson's baby powder, the use of Johnson's</p> <p>19 baby powder.</p> <p>20 Q. And the opinion you hold based</p> <p>21 on Johnson's baby powder, does that take into</p> <p>22 account the presence or absence of asbestos?</p> <p>23 MS. MILLER: Objection. Asked,</p> <p>24 answered and confusing.</p> <p>25 THE WITNESS: I assume nothing</p>	<p style="text-align: right;">Page 80</p> <p>1 on the pathomechanism of ovarian cancer?</p> <p>2 A. I don't believe pathomechanism</p> <p>3 is a word, but I'll give you a chance to</p> <p>4 rephrase it. Otherwise, I'll make my best</p> <p>5 attempt to infer what you were asking.</p> <p>6 Q. Has your research ever focused</p> <p>7 on the cause of ovarian cancer?</p> <p>8 A. How do you define "cause"?</p> <p>9 Q. As we go through today's</p> <p>10 deposition, I'd like to use your definition</p> <p>11 so you're most comfortable with it.</p> <p>12 How would you define a cause?</p> <p>13 MS. MILLER: Objection. Vague.</p> <p>14 THE WITNESS: It's impossible</p> <p>15 to answer.</p> <p>16 QUESTIONS BY MR. RESTAINO:</p> <p>17 Q. By whom?</p> <p>18 A. Me.</p> <p>19 Q. And why is that?</p> <p>20 A. Because cause has a multitude</p> <p>21 of meanings.</p> <p>22 Q. If I walk into this room at</p> <p>23 night and the light is off and it's dark and</p> <p>24 I flip the switch on, did I cause the light</p> <p>25 to go on?</p>
<p style="text-align: right;">Page 79</p> <p>1 other than what I read on the bottle</p> <p>2 about Johnson's baby powder.</p> <p>3 QUESTIONS BY MR. RESTAINO:</p> <p>4 Q. Do you know if Johnson &amp;</p> <p>5 Johnson has any documentation of studies that</p> <p>6 they have performed showing the presence of</p> <p>7 asbestos in their talcum powder?</p> <p>8 A. I'm not aware of any studies</p> <p>9 that Johnson &amp; Johnson has ever performed on</p> <p>10 anything.</p> <p>11 Q. Am I correct in understanding</p> <p>12 that as of today you are chair, department of</p> <p>13 human molecular genetics?</p> <p>14 A. At the Herbert Wertheim College</p> <p>15 of Medicine of Florida International</p> <p>16 University, yes, I'm a tenured professor and</p> <p>17 chair.</p> <p>18 Q. Are you also there an associate</p> <p>19 dean for basic research in graduate programs?</p> <p>20 A. Yes.</p> <p>21 Q. And are you professor of</p> <p>22 obstetrics and gynecology at the Herbert</p> <p>23 Wertheim College of Medicine?</p> <p>24 A. Yes.</p> <p>25 Q. Is your research ever focused</p>	<p style="text-align: right;">Page 81</p> <p>1 MS. MILLER: Objection.</p> <p>2 THE WITNESS: Again, that's a</p> <p>3 very complex question. One could</p> <p>4 argue that the electricity caused the</p> <p>5 light to go on, for example.</p> <p>6 QUESTIONS BY MR. RESTAINO:</p> <p>7 Q. One could argue that the wire</p> <p>8 has to be attached to the switch to the light</p> <p>9 bulb, correct?</p> <p>10 A. Correct.</p> <p>11 Q. One has to assume that the</p> <p>12 light bulb is a working light bulb, correct?</p> <p>13 A. Yes.</p> <p>14 Q. One has to assume that the law</p> <p>15 firm paid its electrical bill, correct?</p> <p>16 A. Correct.</p> <p>17 Q. Are you familiar with the</p> <p>18 multifactorial basis of disease?</p> <p>19 MS. MILLER: Objection.</p> <p>20 THE WITNESS: That is a, with</p> <p>21 all due respect, fabulously broad</p> <p>22 question.</p> <p>23 QUESTIONS BY MR. RESTAINO:</p> <p>24 Q. I think we'll revisit it.</p> <p>25 A. Which disease?</p>

21 (Pages 78 to 81)



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<p style="text-align: right;">Page 82</p> <p>1 Q. Ovarian cancer.</p> <p>2 A. So could you repeat the</p> <p>3 question with a more specific disease in</p> <p>4 mind, please?</p> <p>5 Q. Sure.</p> <p>6 Are you familiar with the</p> <p>7 multi -- what has been described as the</p> <p>8 multifactorial basis of ovarian cancer?</p> <p>9 A. I would have to say that I'm</p> <p>10 familiar in very general terms with the</p> <p>11 multifactorial basis of all human cancers,</p> <p>12 which would include ovarian.</p> <p>13 Q. Okay. Has your research ever</p> <p>14 focused on the epidemiology regarding chronic</p> <p>15 inflammation and the development of cancer?</p> <p>16 MS. MILLER: Objection.</p> <p>17 THE WITNESS: No.</p> <p>18 QUESTIONS BY MR. RESTAINO:</p> <p>19 Q. And --</p> <p>20 A. I'm sorry. And by research,</p> <p>21 I'm assuming you're referring to my own</p> <p>22 laboratory-based research?</p> <p>23 Q. Once again, I want to make sure</p> <p>24 we're using terms that you're most</p> <p>25 comfortable with.</p>	<p style="text-align: right;">Page 84</p> <p>1 MS. MILLER: Objection.</p> <p>2 THE WITNESS: I'm only prepared</p> <p>3 to answer that question in very</p> <p>4 general terms in the sense that my</p> <p>5 understanding of epidemiology is to</p> <p>6 study association of X and Y as</p> <p>7 opposed to causation. I distinguish</p> <p>8 association from causation.</p> <p>9 QUESTIONS BY MR. RESTAINO:</p> <p>10 Q. Does a randomized controlled</p> <p>11 trial establish causation in certain</p> <p>12 circumstances?</p> <p>13 MS. MILLER: Objection.</p> <p>14 THE WITNESS: It's a very vague</p> <p>15 and convoluted question that's</p> <p>16 impossible for me to answer.</p> <p>17 QUESTIONS BY MR. RESTAINO:</p> <p>18 Q. And is that because you're not</p> <p>19 an expert in epidemiology?</p> <p>20 MS. MILLER: Objection.</p> <p>21 THE WITNESS: I'm very familiar</p> <p>22 with the concept of clinical trials.</p> <p>23 I sat on the committee for</p> <p>24 experimental medicine for the</p> <p>25 gynecologic oncology group for</p>
<p style="text-align: right;">Page 83</p> <p>1 So do you do, for lack of a</p> <p>2 better description, bench-type of</p> <p>3 pharmacological research or genetic research?</p> <p>4 A. Certainly I don't do</p> <p>5 pharmacological bench research. I have for</p> <p>6 many years done molecular genetic and genetic</p> <p>7 research.</p> <p>8 I guess my reason for asking</p> <p>9 the question was because lawyers seem to use</p> <p>10 the term "research" referring to preparation</p> <p>11 for expert testimony in a deposition context.</p> <p>12 Q. In your professional setting,</p> <p>13 without lawyers being in the room, would your</p> <p>14 research also consist of analysis of the</p> <p>15 existing medical literature?</p> <p>16 MS. MILLER: Objection.</p> <p>17 THE WITNESS: I just find that,</p> <p>18 I'm sorry, a very weird question.</p> <p>19 I've never met a biomedical scientist</p> <p>20 who didn't read the literature.</p> <p>21 QUESTIONS BY MR. RESTAINO:</p> <p>22 Q. Do you agree or disagree that</p> <p>23 the epidemiologic evidence implicates chronic</p> <p>24 inflammation as a central mechanism in the</p> <p>25 pathogenesis of ovarian cancer?</p>	<p style="text-align: right;">Page 85</p> <p>1 17 years, and I can assure you that we</p> <p>2 rarely discuss epidemiology in the</p> <p>3 design of clinical trials.</p> <p>4 QUESTIONS BY MR. RESTAINO:</p> <p>5 Q. Okay. Do you agree or disagree</p> <p>6 that rapid cell division increases the</p> <p>7 possibility for DNA replication error?</p> <p>8 MS. MILLER: Objection.</p> <p>9 THE WITNESS: Again, a very</p> <p>10 vague question, but I'll offer an</p> <p>11 opinion. DNA replication error is</p> <p>12 impossible absent cell division.</p> <p>13 QUESTIONS BY MR. RESTAINO:</p> <p>14 Q. So would you agree that the</p> <p>15 possibility for DNA replication error is</p> <p>16 increased with rapid cell division?</p> <p>17 A. I'll give you the same answer:</p> <p>18 Cell division is required for errors in DNA</p> <p>19 replication.</p> <p>20 Q. Okay. Would you agree or</p> <p>21 disagree that rapid cell division increases</p> <p>22 the possibility of ineffective DNA repair?</p> <p>23 A. It's the same question asked in</p> <p>24 a different fashion, and I've answered it</p> <p>25 twice, with all due respect.</p>

22 (Pages 82 to 85)

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<p style="text-align: right;">Page 86</p> <p>1 MS. MILLER: With all due 2 respect, you didn't give me a chance 3 to object that it was asked and 4 answered. 5 THE WITNESS: So noted. 6 QUESTIONS BY MR. RESTAINO: 7 Q. Do you agree or disagree that 8 rapid cell division increases the possibility 9 of subsequent mutation? 10 MS. MILLER: Objection. 11 THE WITNESS: Same question. 12 Answered. 13 QUESTIONS BY MR. RESTAINO: 14 Q. Okay. Now, the expert report 15 that I believe you still have in front of 16 you, did you write the entire expert report 17 yourself? 18 A. Yes. 19 Q. Did you do the -- any research 20 that you needed to do for your expert report 21 by yourself? 22 A. Yes. 23 Q. In your general scientific 24 publications, do you utilize research 25 assistants, post-grad fellows, individuals</p>	<p style="text-align: right;">Page 88</p> <p>1 A. I can only accurately answer 2 that question by asking you a question. 3 Q. Yes, sir. 4 A. When you say "medical 5 literature," do you mean medical and 6 scientific literature? 7 Q. Yes, please. Let me correct 8 that. 9 And going forward for today, 10 would it be more comfortable for you to be -- 11 to refer to it as the scientific literature, 12 to encompass both medical and scientific, or 13 would you like them bifurcated? 14 What would be most comfortable 15 for you? 16 A. The term I prefer is biomedical 17 literature. 18 Q. Biomedical? 19 A. Yes. 20 Q. Did you do the biomedical 21 research yourself prior to writing your 22 expert report? 23 MS. MILLER: Objection. 24 THE WITNESS: Yes. 25</p>
<p style="text-align: right;">Page 87</p> <p>1 like that? 2 A. I'm sorry, please repeat the 3 question. 4 Q. Yes. 5 In your professional life, if 6 you're going to be writing a review article 7 or an original piece, do you utilize post-doc 8 fellows, residents, research fellows, any 9 individuals like that that are still in 10 training to assist you in your research? 11 A. Yes. 12 Q. And did any of those type of 13 individuals assist you with the research 14 necessary to write your expert report today? 15 A. No. 16 Q. Okay. Did you review germane 17 medical literature for -- prior to writing 18 your expert report? 19 A. Well, I don't think I reviewed 20 non-germane medical or scientific literature, 21 so I suppose the default answer is yes. 22 Q. Okay. Well, what methodology 23 did you employ in order to conduct your 24 research of the medical literature prior to 25 writing your expert report?</p>	<p style="text-align: right;">Page 89</p> <p>1 QUESTIONS BY MR. RESTAINO: 2 Q. And what was the methodology 3 that you employed? 4 A. Well, other than reading expert 5 reports and deposition transcripts, which I 6 think we can all agree were provided for me, 7 I think I utilized a methodology that most 8 would agree is standard, which would involve 9 PubMed searches and perhaps to a lesser 10 extent Google searches. 11 Q. In conducting your PubMed and 12 perhaps to a lesser extent Google searches, 13 did you utilize keywords to find the 14 particular articles you may have been looking 15 for? 16 A. I'm not aware of any other way 17 to do a search without keywords. 18 Q. And as you sit here today, can 19 you share with us some of the keywords you 20 utilized? 21 A. "Ovarian," "cancer," "talc," 22 "talcum powder." I honestly don't remember 23 any other words. 24 Q. How about "inflammation"? 25 A. So I'm aware of having come</p>

23 (Pages 86 to 89)

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<p style="text-align: right;">Page 90</p> <p>1 across papers having to do with, for example,  2 inflammation insofar as the keywords that I  3 recall using led me to papers that had  4 concepts embedded in them as perhaps  5 citations, which would lead me to look up a  6 citation typically with an author's name, a  7 page number, a journal, for example.  8 I don't recall performing a  9 literature search using the term  10 "inflammation" specifically.  11 Q. Forgive me for paraphrasing an  12 earlier answer you may have given, but my  13 understanding was that your understanding for  14 your purpose of being here today was to  15 discuss Dr. Saed's expert report and his  16 experiment and the biological plausibility as  17 put forth by the plaintiff attorneys.  18 Am I wrong with that?  19 MS. MILLER: Objection.  20 THE WITNESS: It's my  21 understanding that my purpose for  22 being here today is to discuss  23 Dr. Saed's work, his published work,  24 his deposition transcript, his expert  25 report specifically, and in a more</p>	<p style="text-align: right;">Page 92</p> <p>1 with the role of inflammation?  2 A. He -- I'm sorry, repeat the  3 question, please.  4 Q. Did Dr. Saed's experiment  5 pertaining to biological plausibility involve  6 the role of inflammation?  7 A. He claims that it did.  8 Q. And I believe you testified  9 earlier that you either read or skimmed the  10 study that was authored by Dr. Shih and  11 attached to his expert report; is that  12 correct?  13 A. I took a very quick look at it.  14 Q. Do you know -- I'm sorry,  15 forgive me.  16 Were you finished?  17 A. Yes.  18 Q. Do you know if a component of  19 that study had to do with the  20 histopathological analysis of the presence or  21 absence of inflammation?  22 A. I honestly can't recall.  23 Q. Did you write in its entirety  24 your expert report by yourself?  25 A. I'm pretty sure you asked</p>
<p style="text-align: right;">Page 91</p> <p>1 general sense biologic plausibility.  2 QUESTIONS BY MR. RESTAINO:  3 Q. Okay. And you understand that  4 a key component of the biological  5 plausibility argument put forth by the  6 plaintiff experts involves the role of  7 chronic inflammation in the development of  8 ovarian cancer?  9 MS. MILLER: Objection.  10 THE WITNESS: I'm sorry, could  11 you repeat the question?  12 QUESTIONS BY MR. RESTAINO:  13 Q. You understand that a key  14 component of the biological plausibility  15 argument put forth by the plaintiff experts  16 involves the role of chronic inflammation in  17 the development of ovarian cancer?  18 MS. MILLER: Objection.  19 THE WITNESS: I can certainly  20 say that I'm most familiar with  21 Dr. Saed's work addressing hypotheses  22 related to biologic plausibility.  23 QUESTIONS BY MR. RESTAINO:  24 Q. Did Dr. Saed's work pertaining  25 to the biological plausibility have to deal</p>	<p style="text-align: right;">Page 93</p> <p>1 before, and I said yes.  2 Q. Okay. Are the words and the  3 language in your report your choice of  4 language?  5 A. It's the same question, but,  6 yes.  7 Q. Are all your opinions that you  8 will be offering regarding the role of  9 Dr. Saed's report and study and the role of  10 biological plausibility contained within your  11 expert report?  12 A. I'm sorry, I thought you were  13 heading somewhere else with the prelude.  14 Could you repeat the question,  15 please?  16 Q. Are all the opinions you will  17 be offering regarding the role of Dr. Saed's  18 report and study and the role of biological  19 plausibility contained within your expert  20 report?  21 A. I'm sure my expert report could  22 have been longer, so that's really a  23 difficult question to answer.  24 Q. As you sit here today, do you  25 have any other opinions that you have not put</p>

24 (Pages 90 to 93)

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<p style="text-align: right;">Page 94</p> <p>1 into your expert report regarding Dr. Saed --</p> <p>2 A. That's just -- I'm sorry for</p> <p>3 laughing. It's a serious -- you're a serious</p> <p>4 man. I'm a serious man. It's a serious</p> <p>5 issue.</p> <p>6 But I just find it an</p> <p>7 incredibly difficult question to answer, I'm</p> <p>8 sorry.</p> <p>9 Q. I'm going to try to make it as</p> <p>10 easy as possible.</p> <p>11 Other than that which you've</p> <p>12 written in your expert report, since the date</p> <p>13 of signing your report, have you established</p> <p>14 any other opinion regarding Dr. Saed's study,</p> <p>15 Dr. Saed's expert report or the biological</p> <p>16 plausibility regarding talcum powder and</p> <p>17 ovarian cancer?</p> <p>18 MS. MILLER: Objection.</p> <p>19 THE WITNESS: Well, I've read</p> <p>20 Dr. Saed's subsequent published paper</p> <p>21 in Reproductive Sciences, which</p> <p>22 happened after I prepared my expert</p> <p>23 report, and I've formed some opinions</p> <p>24 about the content of that paper.</p> <p>25</p>	<p style="text-align: right;">Page 96</p> <p>1 other expert opinion you've developed since</p> <p>2 you've signed your expert report that you</p> <p>3 would be offering. And we have a right to</p> <p>4 know what that expert opinion is.</p> <p>5 A. I'll do my best to answer</p> <p>6 whichever questions you choose to ask me. I</p> <p>7 think about this a lot.</p> <p>8 Q. Have --</p> <p>9 A. In the middle of the night, for</p> <p>10 example.</p> <p>11 I can't honestly say that I'm</p> <p>12 forming expert opinions, but, you know, it's</p> <p>13 consumed a lot of my free time over the past</p> <p>14 several months.</p> <p>15 Q. As you've thought about this</p> <p>16 since you've signed and submitted your expert</p> <p>17 report, have you developed any opinions that</p> <p>18 are in disagreement with that which you have</p> <p>19 listed in your expert report?</p> <p>20 A. No.</p> <p>21 Q. Do you consider yourself an</p> <p>22 expert in the carcinogenicity of ovarian</p> <p>23 cancer?</p> <p>24 MS. MILLER: Objection.</p> <p>25 THE WITNESS: And so I suppose</p>
<p style="text-align: right;">Page 95</p> <p>1 QUESTIONS BY MR. RESTAINO:</p> <p>2 Q. Okay. Are those opinions</p> <p>3 listed in your expert report?</p> <p>4 MS. MILLER: Objection.</p> <p>5 THE WITNESS: You obviously</p> <p>6 misunderstood my answer.</p> <p>7 QUESTIONS BY MR. RESTAINO:</p> <p>8 Q. Well, you said -- what you said</p> <p>9 was, "Well, I read Dr. Saed's subsequent</p> <p>10 published paper in Reproductive Sciences,</p> <p>11 which happened after I prepared my expert</p> <p>12 report."</p> <p>13 Was that, after you prepared</p> <p>14 it, also after you finalized it and signed</p> <p>15 it?</p> <p>16 MS. MILLER: As you know, it</p> <p>17 wasn't published until after</p> <p>18 February 25, so I don't really know</p> <p>19 where you're headed here.</p> <p>20 MR. RESTAINO: So I</p> <p>21 misunderstood, and I'll strike the</p> <p>22 question.</p> <p>23 QUESTIONS BY MR. RESTAINO:</p> <p>24 Q. Doctor, I'm just trying to</p> <p>25 learn if there's anything else that -- any</p>	<p style="text-align: right;">Page 97</p> <p>1 when I ask you, how do you define</p> <p>2 carcinogenicity, you're going to ask</p> <p>3 me how do I define carcinogenicity?</p> <p>4 QUESTIONS BY MR. RESTAINO:</p> <p>5 Q. I'm going to fool you this</p> <p>6 time.</p> <p>7 How about carcinogenicity is</p> <p>8 the ability or tendency of an agent to induce</p> <p>9 tumors, benign or malignant, increase their</p> <p>10 incidence or malignancy, or shorten the time</p> <p>11 of tumor occurrence when it is inhaled,</p> <p>12 ingested, dermally applied or injected, does</p> <p>13 that sound like a reasonable definition?</p> <p>14 A. That's the Google dictionary</p> <p>15 definition.</p> <p>16 Q. I disagree, but it's a</p> <p>17 definition.</p> <p>18 A. It's certainly a definition.</p> <p>19 Q. Is it a reasonable definition?</p> <p>20 A. It's a reasonable definition.</p> <p>21 Q. Okay. Are you familiar with</p> <p>22 what has been described as the hallmarks of</p> <p>23 carcinogenicity as published by Hanahan and</p> <p>24 Weinberg in 1990?</p> <p>25 A. No.</p>

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<p style="text-align: right;">Page 98</p> <p>1 You got the title wrong, and</p> <p>2 you got the date wrong.</p> <p>3 Q. How so?</p> <p>4 A. They've published two versions,</p> <p>5 one in 2000 and one in 2011, and</p> <p>6 carcinogenicity is not in the title.</p> <p>7 Q. I wasn't actually asking for</p> <p>8 the title of the paper, but are you -- you're</p> <p>9 obviously then familiar with Hallmarks of</p> <p>10 Cancer as published in 1990?</p> <p>11 A. No.</p> <p>12 Q. Is there a different title?</p> <p>13 A. No, there's a different date.</p> <p>14 Q. 2000. I'm sorry, in 2000.</p> <p>15 A. It's okay.</p> <p>16 I have very little memory of</p> <p>17 the original 2000 paper. I've certainly read</p> <p>18 the paper published -- the update, the</p> <p>19 version of the paper published in 2011.</p> <p>20 Q. As you sit here today, can you</p> <p>21 share with us any of the recognized hallmarks</p> <p>22 of cancer?</p> <p>23 MS. MILLER: Objection.</p> <p>24 THE WITNESS: I'd be happy to</p> <p>25 go over them with you if you could</p>	<p style="text-align: right;">Page 100</p> <p>1 attorneys in a previous deposition</p> <p>2 transcript, but I'll let you recapitulate the</p> <p>3 number for me, if that's what you're</p> <p>4 interested in doing.</p> <p>5 Q. I'll come back.</p> <p>6 A. Okay.</p> <p>7 Q. We've talked a little bit about</p> <p>8 a risk factor, correct?</p> <p>9 A. I seem to recall the question</p> <p>10 as to how do I define a risk factor, yeah.</p> <p>11 Q. Do you agree that there are</p> <p>12 certain risk factors that are associated with</p> <p>13 the development of ovarian cancer?</p> <p>14 A. Yes.</p> <p>15 Q. Would you agree that for a risk</p> <p>16 factor to be a true risk factor, it must be</p> <p>17 biologically plausible?</p> <p>18 A. "True" is an overly subjective</p> <p>19 and impossible to interpret term from a</p> <p>20 scientist's -- from a scientific standpoint.</p> <p>21 Q. Would you agree that for a risk</p> <p>22 factor to be an accurate risk factor, it must</p> <p>23 be biologically plausible?</p> <p>24 A. Same answer.</p> <p>25 Q. Would you agree that a risk</p>
<p style="text-align: right;">Page 99</p> <p>1 produce a copy of the paper. It's a</p> <p>2 extraordinarily comprehensive overview</p> <p>3 of cancer generally that's typically</p> <p>4 used to inform nonexperts in the</p> <p>5 field.</p> <p>6 QUESTIONS BY MR. RESTAINO:</p> <p>7 Q. What is the objective basis for</p> <p>8 your opinion that it is typically used to</p> <p>9 inform nonexperts in the field?</p> <p>10 A. Experts in the field of cancer</p> <p>11 generally are familiar with the concepts</p> <p>12 articulated by the authors.</p> <p>13 I, for example, use Figure 1</p> <p>14 when I'm giving lectures to lay people,</p> <p>15 general practitioners, medical students, for</p> <p>16 example.</p> <p>17 Q. And how about other</p> <p>18 researchers? Do you know how they use the</p> <p>19 publication?</p> <p>20 A. I certainly can't speak to how</p> <p>21 other researchers use any publication.</p> <p>22 Q. Do you know how often that</p> <p>23 paper has been cited by medical researchers?</p> <p>24 A. I could try to recall the</p> <p>25 number that was offered by plaintiffs'</p>	<p style="text-align: right;">Page 101</p> <p>1 factor for the development of a disease such</p> <p>2 as ovarian cancer must have a biologically</p> <p>3 plausible basis in order to be an accurate</p> <p>4 risk?</p> <p>5 A. Reusing the same words, so I</p> <p>6 would have to give you the same answer.</p> <p>7 Q. I'm just trying to make it</p> <p>8 easier for you. Let me try using an example.</p> <p>9 Would you agree that aside from</p> <p>10 gender, which is a given, that a woman over</p> <p>11 age 45 is at increased risk for developing</p> <p>12 ovarian cancer than a woman in her 20s?</p> <p>13 MS. MILLER: Objection.</p> <p>14 THE WITNESS: A great majority</p> <p>15 of human cancers, other than those</p> <p>16 that occur in kids, which are very</p> <p>17 limited in scope, are diseases of</p> <p>18 aging, generally speaking. So age is,</p> <p>19 in and of itself, a risk factor for</p> <p>20 virtually all cancers that occur in</p> <p>21 adults.</p> <p>22 QUESTIONS BY MR. RESTAINO:</p> <p>23 Q. Is age a biologically plausible</p> <p>24 risk factor?</p> <p>25 MS. MILLER: Objection.</p>

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<p style="text-align: right;">Page 102</p> <p>1 THE WITNESS: Yes.</p> <p>2 QUESTIONS BY MR. RESTAINO:</p> <p>3 Q. How about a woman of Jewish</p> <p>4 ethnicity? Does a woman over the age of 55</p> <p>5 who is of Jewish ethnicity have an increased</p> <p>6 risk for the development of ovarian cancer</p> <p>7 than a non-Jewish woman who is in her 20s?</p> <p>8 MS. MILLER: Objection.</p> <p>9 THE WITNESS: Ashkenazi</p> <p>10 Jewish --</p> <p>11 QUESTIONS BY MR. RESTAINO:</p> <p>12 Q. If you like.</p> <p>13 A. -- question mark?</p> <p>14 Q. Yes.</p> <p>15 MS. MILLER: Still objection.</p> <p>16 THE WITNESS: You've conflated</p> <p>17 two questions into one, I'm sorry.</p> <p>18 You've -- you've asked about</p> <p>19 Jewish women of a certain age and</p> <p>20 non-Jewish women of a certain age.</p> <p>21 Could we break -- could we</p> <p>22 parse out the question?</p> <p>23 QUESTIONS BY MR. RESTAINO:</p> <p>24 Q. Are women of Jewish ethnicity</p> <p>25 at a higher risk of developing ovarian cancer</p>	<p style="text-align: right;">Page 104</p> <p>1 A. Thank you.</p> <p>2 Q. -- in 2013 do you recall</p> <p>3 publishing "Metastasis Dynamics for a</p> <p>4 Non-Small-Cell Lung Cancer: Effect of</p> <p>5 Patient and Tumor-Related Factors"?</p> <p>6 A. I'm sorry, I -- no.</p> <p>7 Q. Okay. Fair enough.</p> <p>8 Would you agree that some of</p> <p>9 the pathological factors that are associated</p> <p>10 with reoccurrence of cancer, specifically</p> <p>11 lung cancer, would be, A, size of the primary</p> <p>12 tumor?</p> <p>13 A. I'm not an expert in lung</p> <p>14 cancer.</p> <p>15 Q. Would it be the same answer</p> <p>16 for -- if there was lymph node involvement?</p> <p>17 MS. MILLER: Objection.</p> <p>18 Same answer to what? Could you</p> <p>19 just make that question clearer?</p> <p>20 MR. RESTAINO: Sure. Sure.</p> <p>21 QUESTIONS BY MR. RESTAINO:</p> <p>22 Q. Would you agree that one of the</p> <p>23 pathological factors associated with a higher</p> <p>24 risk of reoccurrence in any cancer, but let's</p> <p>25 limit it to non-small cell lung cancer, would</p>
<p style="text-align: right;">Page 103</p> <p>1 than women of non-Jewish ethnicity?</p> <p>2 MS. MILLER: Objection.</p> <p>3 THE WITNESS: Ashkenazi Jews,</p> <p>4 generally speaking, carry mutations in</p> <p>5 the BRCA1 and 2 genes at a much higher</p> <p>6 frequency than individuals in the</p> <p>7 non-Ashkenazi Jewish population.</p> <p>8 MS. MILLER: Stop reminding me.</p> <p>9 THE WITNESS: And I would</p> <p>10 remind you that men do as well, of the</p> <p>11 same ethnicity.</p> <p>12 QUESTIONS BY MR. RESTAINO:</p> <p>13 Q. But men are not at a risk for</p> <p>14 ovarian cancer, correct?</p> <p>15 A. No, but they're certainly at</p> <p>16 risk for male breast cancer, which is</p> <p>17 associated with BRCA2 in particular.</p> <p>18 Q. BRCA1 and 2, are they</p> <p>19 biologically plausible risk factors for the</p> <p>20 development of ovarian cancer in women?</p> <p>21 A. Yes.</p> <p>22 Q. Doctor, you've written also on</p> <p>23 the risk factors of carcinogenicity. And</p> <p>24 without playing any word games or trying to</p> <p>25 ask you when and where --</p>	<p style="text-align: right;">Page 105</p> <p>1 include lymph node involvement?</p> <p>2 A. I would agree that the risk of</p> <p>3 recurrence of virtually all human cancers is</p> <p>4 increased with higher stage, and lymph node</p> <p>5 involvement is typically associated with a</p> <p>6 higher pathologic or -- and/or clinical</p> <p>7 stage.</p> <p>8 Q. Is that a biologically</p> <p>9 plausible risk factor for reoccurrence?</p> <p>10 A. Could you ask the complete</p> <p>11 question, please?</p> <p>12 Q. Would the lymph node</p> <p>13 involvement of any cancer be associated with</p> <p>14 a biologically plausible increased risk of</p> <p>15 reoccurrence of that cancer?</p> <p>16 A. Yes.</p> <p>17 Q. And as a physician -- excuse</p> <p>18 me. As scientist of your gravitas, would you</p> <p>19 agree that you would not publish the risk</p> <p>20 factors of any cancer, whether it be the</p> <p>21 origin of the cancer or the reoccurrence, if</p> <p>22 the risk factor did not have a biologically</p> <p>23 plausible basis; is that a fair enough</p> <p>24 statement?</p> <p>25 MS. MILLER: Objection.</p>

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<p style="text-align: right;">Page 106</p> <p>1 THE WITNESS: Well, I hope it's</p> <p>2 a question, first of all.</p> <p>3 And could you please repeat it?</p> <p>4 QUESTIONS BY MR. RESTAINO:</p> <p>5 Q. Yes.</p> <p>6 Doctor, as a scientist with</p> <p>7 your gravitas --</p> <p>8 A. Thank you.</p> <p>9 Q. -- would you agree you would</p> <p>10 not publish in the peer-reviewed medical --</p> <p>11 biomedical literature on the risk factor of</p> <p>12 any cancer, be it may -- be as it may the</p> <p>13 origin of that cancer or the reoccurrence of</p> <p>14 that cancer unless the risk factors had a</p> <p>15 biologically plausible basis?</p> <p>16 MS. MILLER: Objection.</p> <p>17 THE WITNESS: I would say that</p> <p>18 generally speaking, biological</p> <p>19 plausibility in the context of cancer</p> <p>20 generally is more important when the</p> <p>21 level of risk associated with the</p> <p>22 hypothesized risk factor is very low.</p> <p>23 So in other words, to give you</p> <p>24 an example, I would suggest that</p> <p>25 biological plausibility linking</p>	<p style="text-align: right;">Page 108</p> <p>1 It's not a memory test, as I</p> <p>2 recall.</p> <p>3 Q. No, it isn't, and I'm not going</p> <p>4 to test your memory in areas there.</p> <p>5 Have you published in the</p> <p>6 biomedical literature on the role of the</p> <p>7 BRCA1 and BRCA2 mutations and their role with</p> <p>8 breast cancer?</p> <p>9 A. Yes.</p> <p>10 Q. Have you published with those</p> <p>11 mutations and their role in ovarian cancer?</p> <p>12 A. Yes.</p> <p>13 Q. Have you published on the role</p> <p>14 of Jewish ethnicity and the development of</p> <p>15 ovarian cancer?</p> <p>16 A. Jewish ethnicity, per se, no.</p> <p>17 Q. And how about any specific type</p> <p>18 of form of Jewish ethnicity?</p> <p>19 A. I'm not getting at Ashkenazi</p> <p>20 versus Sephardic. I'm getting at ethnicity,</p> <p>21 per se, as opposed to the prevalence of BRCA</p> <p>22 mutations in the Ashkenazi.</p> <p>23 Q. Regarding the development of</p> <p>24 ovarian cancer, do you recognize family</p> <p>25 history as a biologically plausible risk</p>
<p style="text-align: right;">Page 107</p> <p>1 cigarette smoking to lung cancer is</p> <p>2 less important because of the enormous</p> <p>3 magnitude of the association,</p> <p>4 consistent and large over decades of</p> <p>5 study.</p> <p>6 QUESTIONS BY MR. RESTAINO:</p> <p>7 Q. Using cigarette smoking --</p> <p>8 A. As an example. I'm sorry to</p> <p>9 interrupt.</p> <p>10 Q. I'm sorry.</p> <p>11 Using cigarette smoking also an</p> <p>12 as example then, cigarette smoking is also</p> <p>13 associated with cardiovascular disease; would</p> <p>14 you agree?</p> <p>15 A. Yes.</p> <p>16 Q. Would you also agree that the</p> <p>17 risk ratio associated with cigarette smoking</p> <p>18 and cardiovascular disease is far less than</p> <p>19 the risk ratio of cigarette smoking and lung</p> <p>20 cancer?</p> <p>21 A. I can't comment on the</p> <p>22 relative -- I can't comment with authority on</p> <p>23 the magnitude of the risk factors for</p> <p>24 cardiovascular disease compared to lung</p> <p>25 cancer associated with cigarette smoking.</p>	<p style="text-align: right;">Page 109</p> <p>1 factor?</p> <p>2 MS. MILLER: Objection.</p> <p>3 THE WITNESS: Well, you're</p> <p>4 using the word "biological</p> <p>5 plausibility" with "risk factor,"</p> <p>6 which is, I have to say, a strange</p> <p>7 concept for me.</p> <p>8 I'm familiar with the concept</p> <p>9 of getting from association in an</p> <p>10 epidemiologic context to causality in</p> <p>11 a biological context using biological</p> <p>12 plausibility as a tool when and, in</p> <p>13 context, where it may be most</p> <p>14 necessary.</p> <p>15 QUESTIONS BY MR. RESTAINO:</p> <p>16 Q. Okay. And in using the term as</p> <p>17 you're most familiar with it, would you</p> <p>18 publish on risk factors for any cancer if, in</p> <p>19 your opinion, that risk factor was not</p> <p>20 biologically plausible?</p> <p>21 MS. MILLER: Objection.</p> <p>22 THE WITNESS: It's just a very</p> <p>23 vague question. Hard to answer.</p> <p>24 If you'd like to refer me to</p> <p>25 one of my specific publications, I'd</p>

28 (Pages 106 to 109)

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<p style="text-align: right;">Page 110</p> <p>1 be happy to address the rationale</p> <p>2 underlying my reasons for publishing</p> <p>3 the data contained in that</p> <p>4 publication.</p> <p>5 QUESTIONS BY MR. RESTAINO:</p> <p>6 Q. Well, I mentioned previously</p> <p>7 the "Metastasis Dynamics for Non-Small-Cell</p> <p>8 Lung Cancer: Effect of Patient and</p> <p>9 Tumor-Related Factors," but as you sit here</p> <p>10 today, you do not recall that, correct?</p> <p>11 A. All I heard, with all due</p> <p>12 respect, sir, is a jumble of words. It</p> <p>13 doesn't even sound like the title of a paper.</p> <p>14 But to the extent that you're</p> <p>15 probably reading from my CV, I don't recall</p> <p>16 the paper.</p> <p>17 Q. Okay.</p> <p>18 MS. MILLER: Is this a good</p> <p>19 time for a break?</p> <p>20 MR. RESTAINO: Sure.</p> <p>21 MS. MILLER: Great.</p> <p>22 VIDEOGRAPHER: Off the record</p> <p>23 at 11:16 a.m.</p> <p>24 (Off the record at 11:16 a.m.)</p> <p>25 VIDEOGRAPHER: We are back on</p>	<p style="text-align: right;">Page 112</p> <p>1 which talc causes the transformation of a</p> <p>2 normal cell into a cell that ultimately</p> <p>3 manifests as the multiple different tumor</p> <p>4 types that we collectively refer to as</p> <p>5 epithelial ovarian carcinoma.</p> <p>6 Q. And have you ever been asked in</p> <p>7 your professional career to review another</p> <p>8 expert's expert report?</p> <p>9 A. Before this litigation?</p> <p>10 Q. Yes, sir.</p> <p>11 A. Yes. Again, I would remind you</p> <p>12 of the one other case, other than the</p> <p>13 administrative issues in Miami, in the late</p> <p>14 '90s, early 2000s, which was litigation</p> <p>15 involving -- well, to answer your question,</p> <p>16 yes, several decades ago.</p> <p>17 Q. And also at that time, were you</p> <p>18 asked to review any underlying notebook or</p> <p>19 laboratory documentation that might have been</p> <p>20 used as the basis for any opinions in that</p> <p>21 expert report?</p> <p>22 A. No.</p> <p>23 Q. Have you ever, in your</p> <p>24 professional career, been asked to review the</p> <p>25 notebook and underlying laboratory documents</p>
<p style="text-align: right;">Page 111</p> <p>1 the record at 11:31 a.m.</p> <p>2 QUESTIONS BY MR. RESTAINO:</p> <p>3 Q. Welcome back, Dr. Boyd.</p> <p>4 Dr. Boyd, do you intend to</p> <p>5 offer an opinion as to whether or not talc</p> <p>6 powder particles can migrate to the ovaries?</p> <p>7 A. No.</p> <p>8 Q. Now, with your expert report,</p> <p>9 if you would turn to page 2. And by that I</p> <p>10 mean the numbered page 2. All right?</p> <p>11 You have a Section 2, Scope of</p> <p>12 Report. And the first sentence there: "I</p> <p>13 was asked to opine on Dr. Ghassan Saed's</p> <p>14 expert report based on my experience as a</p> <p>15 molecular biologist in cancer research, and</p> <p>16 in particular, whether this research supports</p> <p>17 the biological plausibility of the</p> <p>18 plaintiff's theory that perineal talc use</p> <p>19 causes ovarian cancer."</p> <p>20 And, Doctor, did I read that</p> <p>21 correctly?</p> <p>22 A. You correctly read those words.</p> <p>23 Q. Now, as you wrote them there,</p> <p>24 how are you using biological plausibility?</p> <p>25 A. The biological process through</p>	<p style="text-align: right;">Page 113</p> <p>1 from an individual's experiments?</p> <p>2 A. Well, that's a pretty broad</p> <p>3 question. I have been the principal</p> <p>4 investigator in many laboratories, and I</p> <p>5 reviewed many laboratory notebooks. I have</p> <p>6 created many laboratory notebooks personally</p> <p>7 in the earlier stages of my career.</p> <p>8 And to reiterate, in the more</p> <p>9 senior stages of my career as a principal</p> <p>10 investigator heading up a laboratory, larger</p> <p>11 or smaller as it might be, I have reviewed a</p> <p>12 multitude of laboratory notebooks, yes.</p> <p>13 Q. Have you ever had -- have you</p> <p>14 ever been asked to review the laboratory</p> <p>15 notebook for any researchers not associated</p> <p>16 with your laboratory?</p> <p>17 A. Yes.</p> <p>18 Q. And under what circumstances?</p> <p>19 A. Alleged scientific fraud at an</p> <p>20 institution where I was in one case the chief</p> <p>21 scientific officer and in another case the</p> <p>22 chair of the department in which the alleged</p> <p>23 fraud took place.</p> <p>24 Q. If you would turn now to --</p> <p>25 stay on page 2 of your expert report. The</p>

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<p style="text-align: right;">Page 114</p> <p>1 top paragraph, third line down, first full 2 sentence you write, "My current research 3 interests." 4 Do you see that, sir? 5 A. Yes. 6 Q. "My current research interests 7 include the histogenesis, open paren, cell of 8 origin, close paren, of ovarian cancer, the 9 comprehensive genomic characterization of 10 ovarian cancer stem cells, and the genomic 11 basis of diethylstilbestrol, open paren, DES, 12 close paren, hyphen, induced carcinogenesis 13 of the cervix and vagina of women exposed to 14 DES in utero." 15 Did I read that correctly? 16 A. You read it perfectly. 17 Q. Okay. Is DES a form of 18 synthetic estrogen? 19 A. DES is indeed a synthetic 20 estrogen. 21 Q. And does the prenatal exposure 22 to DES cause subsequent development of clear 23 cell adenocarcinoma in the lower reproductive 24 tract of some daughters of women who have 25 taken the drug?</p>	<p style="text-align: right;">Page 116</p> <p>1 as opposed to in animals or lower 2 organisms or cells and so forth, in 3 humans we tend to make these 4 conclusions based on the strengths of 5 the association. 6 And in this particular case, 7 clear cell carcinomas of the vagina 8 and cervix are, generally speaking, 9 extremely rare tumors. Furthermore, 10 in young women, for example, 11 teenagers, women in their 20s, they're 12 virtually unheard of. 13 And so in 1971, more or less, 14 when Dr. Arthur Herbst at the 15 University of Chicago published a 16 paper in the New England Journal 17 describing a cluster of cases of clear 18 cell adenocarcinoma of the 19 cervicovaginal region in women exposed 20 to DES in utero, this was such a rare 21 confluence of an environmental, if you 22 will, or biological exposure to a 23 xenobiotic and the development of an 24 otherwise virtually unheard of cancer 25 in terms of the cancer and the age of</p>
<p style="text-align: right;">Page 115</p> <p>1 A. It has been associated with the 2 development of aforementioned tumors in the 3 context that you've described, yes. 4 Q. My question was: "Does the 5 prenatal exposure to DES cause subsequent 6 development of clear cell adenocarcinoma?" 7 And your answer involved the 8 word "association." 9 A. Yes. 10 Q. So let me reask my question, if 11 I may. 12 Does the prenatal exposure to 13 DES cause subsequent development of clear 14 cell adenocarcinoma in the lower reproductive 15 tract of some daughters of women who have 16 taken the drug? 17 MS. MILLER: Objection. 18 THE WITNESS: In humans, for a 19 given human patient, it should be 20 rather self-evident that it's 21 virtually impossible to ascribe -- or 22 attribute, I'm sorry, the development 23 of a particular cancer to a particular 24 exposure in a given individual. 25 So we look typically, in humans</p>	<p style="text-align: right;">Page 117</p> <p>1 the women developing it, that the 2 strength of the association was, in 3 the minds of many at the time, 4 sufficient to attribute causality 5 between the in utero exposure to DES 6 and the development of the clear cell 7 cancer in the young women. 8 I hope that was a cogent answer 9 to your question. 10 QUESTIONS BY MR. RESTAINO: 11 Q. Yes. 12 Do you rely heavily upon 13 strength of association to determine a 14 causation? 15 MS. MILLER: Objection. 16 THE WITNESS: I'm sorry, I was 17 distracted by the -- 18 MS. MILLER: Yeah, is there -- 19 is that on there on purpose? 20 THE WITNESS: I just keep 21 looking at my CV and wondering -- 22 MS. MILLER: With the little 23 green sticky on it? 24 MR. RESTAINO: No. 25 THE WITNESS: I guess it's</p>

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<p style="text-align: right;">Page 118</p> <p>1 the --</p> <p>2 MR. RESTAINO: We can probably</p> <p>3 turn this off.</p> <p>4 THE WITNESS: There's a camera</p> <p>5 there or something.</p> <p>6 MS. MILLER: Well, why don't</p> <p>7 you turn that off, because it is</p> <p>8 distracting.</p> <p>9 THE WITNESS: I apologize.</p> <p>10 MR. RESTAINO: No, there's no</p> <p>11 apology necessary.</p> <p>12 THE WITNESS: Yeah.</p> <p>13 And could you repeat the</p> <p>14 question, please?</p> <p>15 QUESTIONS BY MR. RESTAINO:</p> <p>16 Q. Well, yes.</p> <p>17 My question, you know, was:</p> <p>18 Does the prenatal exposure to DES cause the</p> <p>19 subsequent development of clear cell</p> <p>20 adenocarcinoma in the lower reproductive</p> <p>21 tract in the daughters of women who have</p> <p>22 taken the drug?</p> <p>23 A. Well, again, I respectfully</p> <p>24 submit that I've answered the question. I'll</p> <p>25 answer it again.</p>	<p style="text-align: right;">Page 120</p> <p>1 page 13 of that document.</p> <p>2 A. All right. I'm sorry, let</p> <p>3 me -- could I just look at, for a moment, the</p> <p>4 document in its entirety?</p> <p>5 And which page, please?</p> <p>6 Q. Page 13.</p> <p>7 Actually, let's look on page 15</p> <p>8 of the document. There's a heading there,</p> <p>9 "Chemicals and Hormonal Cancers."</p> <p>10 Do you see that, sir?</p> <p>11 A. Uh-huh.</p> <p>12 Q. Now, in the middle of that</p> <p>13 paragraph, the big paragraph underneath it,</p> <p>14 one, two, three, four, five, six, seven,</p> <p>15 eight -- nine lines down there's a sentence</p> <p>16 that starts all the way to the right with the</p> <p>17 word "much" after a citation of Marselos and</p> <p>18 Tomatis.</p> <p>19 Do you see that, sir?</p> <p>20 A. Yes.</p> <p>21 MS. MILLER: I don't.</p> <p>22 MR. RESTAINO: Page 15,</p> <p>23 Chemicals and Hormonal Cancers,</p> <p>24 Jessica.</p> <p>25 MS. MILLER: Okay.</p>
<p style="text-align: right;">Page 119</p> <p>1 Q. I'm sorry, sir, I only asked</p> <p>2 again because you asked me to.</p> <p>3 MS. MILLER: Actually, that</p> <p>4 wasn't your last question. You had</p> <p>5 moved on from that.</p> <p>6 THE WITNESS: Yeah, it was a</p> <p>7 different question.</p> <p>8 MR. RESTAINO: Okay. I</p> <p>9 apologize.</p> <p>10 QUESTIONS BY MR. RESTAINO:</p> <p>11 Q. Do you rely upon the strength</p> <p>12 of association in determining causation?</p> <p>13 A. I think it's an important</p> <p>14 factor.</p> <p>15 (Boyd Exhibit 6 marked for</p> <p>16 identification.)</p> <p>17 QUESTIONS BY MR. RESTAINO:</p> <p>18 Q. I've now marked as Boyd 6 an</p> <p>19 article titled "Hormonal Carcinogenesis and</p> <p>20 Environmental Influences: Background and</p> <p>21 Overview," written by a James Huff, Jeff Boyd</p> <p>22 and J. Carl Barrett.</p> <p>23 Does that sound familiar, sir?</p> <p>24 A. Yes.</p> <p>25 Q. And if you would turn to</p>	<p style="text-align: right;">Page 121</p> <p>1 MR. RESTAINO: About 11 down.</p> <p>2 The word "much" is on the right-hand</p> <p>3 side following the citation.</p> <p>4 MS. MILLER: I see it.</p> <p>5 QUESTIONS BY MR. RESTAINO:</p> <p>6 Q. "Much of the stimulus for</p> <p>7 evaluating chemicals for potential</p> <p>8 carcinogenicity came from the revelation that</p> <p>9 DES caused cancer in both male and female</p> <p>10 human offspring whose women have been given</p> <p>11 DES to prevent or reduce threatened</p> <p>12 spontaneous abortion."</p> <p>13 And then there's several</p> <p>14 citations there, including Chapter 19 of the</p> <p>15 volume from which this paper came from.</p> <p>16 Did I read that correctly?</p> <p>17 A. Yes.</p> <p>18 Q. And you used -- you write there</p> <p>19 that "DES caused cancer," correct?</p> <p>20 A. Well, first of all, three of</p> <p>21 us, I being the middle author, were involved</p> <p>22 in the authorship of this article.</p> <p>23 So I'm sorry, but I -- I</p> <p>24 focused on the word "you," so I would</p> <p>25 respectfully ask you to repeat the question</p>

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<p style="text-align: right;">Page 122</p> <p>1 so that I may digest the full question.</p> <p>2 Q. As used here by yourself and</p> <p>3 your coauthors, "Much of the stimulus for</p> <p>4 evaluating chemicals for potential</p> <p>5 carcinogenicity came from the revelation that</p> <p>6 DES caused cancer in both male and female</p> <p>7 human offspring whose mother had been given</p> <p>8 DES to prevent or reduce threatened</p> <p>9 spontaneous abortion."</p> <p>10 Did I read it correctly?</p> <p>11 A. You read it correctly again,</p> <p>12 yes.</p> <p>13 Q. Okay. Now, Doctor, has the</p> <p>14 causal association between DES and clear cell</p> <p>15 adenocarcinoma ever been established in a</p> <p>16 randomized controlled trial?</p> <p>17 MS. MILLER: Objection.</p> <p>18 THE WITNESS: I'll just say no.</p> <p>19 QUESTIONS BY MR. RESTAINO:</p> <p>20 Q. Has the causal association</p> <p>21 between DES and clear cell adenocarcinoma</p> <p>22 ever been established in a cohort</p> <p>23 observational study?</p> <p>24 MS. MILLER: Objection.</p> <p>25 THE WITNESS: Could you repeat</p>	<p style="text-align: right;">Page 124</p> <p>1 misleading question.</p> <p>2 THE WITNESS: I would say no</p> <p>3 because -- for the primary reason that</p> <p>4 the -- the events were extraordinarily</p> <p>5 rare, and DES was on the market for</p> <p>6 pregnancy support for a relatively</p> <p>7 short period of time, late '40s until</p> <p>8 1971.</p> <p>9 It would be impossible to do</p> <p>10 such a study, in my mind, and have it</p> <p>11 significantly powered; hence the</p> <p>12 reliance on animal models over the</p> <p>13 years to provide much more rigorous</p> <p>14 evidence of causality with respect to</p> <p>15 DES and carcinogenicity.</p> <p>16 QUESTIONS BY MR. RESTAINO:</p> <p>17 Q. In fact, the initial</p> <p>18 association between DES and clear cell</p> <p>19 carcinoma -- adenocarcinoma in the offspring</p> <p>20 of women who took it, the drug, were</p> <p>21 established in case-control studies</p> <p>22 initially, correct?</p> <p>23 A. I'm of the -- I'm aware of the</p> <p>24 paper that I referenced earlier as being the</p> <p>25 first suggestion that there was an</p>
<p style="text-align: right;">Page 123</p> <p>1 the question, please?</p> <p>2 QUESTIONS BY MR. RESTAINO:</p> <p>3 Q. Yes.</p> <p>4 Has the causal association</p> <p>5 between DES and clear cell adenocarcinoma</p> <p>6 ever been established in a cohort</p> <p>7 observational study?</p> <p>8 A. Well, first of all, you're</p> <p>9 using the words "causal" and "association"</p> <p>10 together, which in my mind are different</p> <p>11 concepts.</p> <p>12 As I believe I suggested</p> <p>13 before, in my mind, epidemiologic studies,</p> <p>14 whether they be case-control or cohort</p> <p>15 studies, are typically relied upon to suggest</p> <p>16 associations leading to hypotheses that may</p> <p>17 be further tested regarding causation.</p> <p>18 So juxtaposing "association"</p> <p>19 and "causation" in the sentence is, in my</p> <p>20 mind, inappropriate.</p> <p>21 Q. Has the causal relationship</p> <p>22 between DES and clear cell adenocarcinoma</p> <p>23 ever been established in a cohort</p> <p>24 observational study?</p> <p>25 MS. MILLER: Objection. It's a</p>	<p style="text-align: right;">Page 125</p> <p>1 association.</p> <p>2 Q. Would you agree it would be</p> <p>3 inaccurate for anyone to say that causation</p> <p>4 cannot be established for the use of</p> <p>5 case-control studies?</p> <p>6 MS. MILLER: Objection.</p> <p>7 THE WITNESS: Several negatives</p> <p>8 in there.</p> <p>9 Could you repeat the question,</p> <p>10 please?</p> <p>11 QUESTIONS BY MR. RESTAINO:</p> <p>12 Q. Would you agree it would be</p> <p>13 inaccurate for one to say that a causal</p> <p>14 association between a substance or a drug and</p> <p>15 the development of cancer cannot be</p> <p>16 established through case-controlled,</p> <p>17 observational epidemiology?</p> <p>18 MS. MILLER: Objection.</p> <p>19 THE WITNESS: Well, first, I'm</p> <p>20 not an expert in epidemiology and</p> <p>21 the -- I'll stop there.</p> <p>22 QUESTIONS BY MR. RESTAINO:</p> <p>23 Q. Okay. You write on the bottom</p> <p>24 of page 2 of your expert report, the very</p> <p>25 last sentence --</p>



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<p style="text-align: right;">Page 126</p> <p>1 MS. MILLER: "Overall?"</p> <p>2 MR. RESTAINO: "Overall."</p> <p>3 QUESTIONS BY MR. RESTAINO:</p> <p>4 Q. The last sentence that goes on</p> <p>5 to page 3. "Overall, genetic predisposition</p> <p>6 is currently believed to be associated with</p> <p>7 approximately 20 percent of all ovarian</p> <p>8 cancers."</p> <p>9 Did I read that correctly?</p> <p>10 A. You read it correctly.</p> <p>11 Q. And then you then write, "It is</p> <p>12 very important to recognize that ovarian</p> <p>13 cancers associated with genetic</p> <p>14 predisposition, as well as those, open paren,</p> <p>15 approximately 80 percent, close paren, that</p> <p>16 occur, quote, sporadically, close paren, are</p> <p>17 all associated with the acquisition and</p> <p>18 accumulation of mutations affecting multiple</p> <p>19 cancer-related genes."</p> <p>20 Did I read that correctly, sir?</p> <p>21 A. You read it correctly.</p> <p>22 Q. And you do not have a reference</p> <p>23 for that opinion, do you?</p> <p>24 A. No.</p> <p>25 Q. The next sense -- next sentence</p>	<p style="text-align: right;">Page 128</p> <p>1 causal mechanism?</p> <p>2 MS. MILLER: Objection.</p> <p>3 THE WITNESS: I would disagree.</p> <p>4 That's a hugely, overly broad</p> <p>5 statement about cancers generally.</p> <p>6 QUESTIONS BY MR. RESTAINO:</p> <p>7 Q. Are you familiar with the term</p> <p>8 "gene environment interaction"?</p> <p>9 A. Yes.</p> <p>10 Q. And this means that an</p> <p>11 environmental factor's effect upon a body may</p> <p>12 depend upon a genetic factor; isn't that</p> <p>13 correct?</p> <p>14 A. Would you repeat the question,</p> <p>15 please?</p> <p>16 Q. That means that an</p> <p>17 environmental factor's effect on the body may</p> <p>18 depend upon a genetic factor; is that</p> <p>19 correct?</p> <p>20 A. Not really.</p> <p>21 Q. You can't think of any</p> <p>22 situations where that --</p> <p>23 A. No, I'm saying your -- your</p> <p>24 definition of the term is not really correct</p> <p>25 as I understand it.</p>
<p style="text-align: right;">Page 127</p> <p>1 you wrote, "In this sense, all ovarian</p> <p>2 cancers, open paren, and indeed all cancers</p> <p>3 generally, close paren, represent a genetic</p> <p>4 disease."</p> <p>5 Did I read that correctly?</p> <p>6 A. Yes, you did.</p> <p>7 Q. And again, there's no reference</p> <p>8 for that, correct?</p> <p>9 A. You are correct.</p> <p>10 Q. Now, are you familiar with the</p> <p>11 term "multicausality" as it relates to cancer</p> <p>12 development?</p> <p>13 A. No.</p> <p>14 Q. Are you associated with the</p> <p>15 term "multicausality" as it relates to any</p> <p>16 disease?</p> <p>17 A. I mean, I can infer what such a</p> <p>18 word might mean. I'm -- it's not a word I've</p> <p>19 ever used.</p> <p>20 Q. Okay.</p> <p>21 A. To the best of my knowledge.</p> <p>22 Q. As an expert in genetics, would</p> <p>23 you agree that it's reasonably safe to assume</p> <p>24 that there are nearly always some genetic and</p> <p>25 some environmental component causes in every</p>	<p style="text-align: right;">Page 129</p> <p>1 Q. Okay. Would you agree that a</p> <p>2 genetic factor's effect on the body may</p> <p>3 depend upon the environmental factor?</p> <p>4 A. Could you give me an example of</p> <p>5 an environmental factor in this particular</p> <p>6 case?</p> <p>7 I assume we're talking about --</p> <p>8 we're still talking about hereditary ovarian</p> <p>9 cancers?</p> <p>10 Q. We're just talking in general</p> <p>11 about the gene environment interaction right</p> <p>12 now and multicausality.</p> <p>13 So, for example, there are</p> <p>14 individuals who smoke 20 -- 20 cigarettes a</p> <p>15 day for 40 years and they develop lung</p> <p>16 cancer, correct?</p> <p>17 A. Correct.</p> <p>18 Q. And there are some individuals</p> <p>19 who smoke the exact same amount and they</p> <p>20 don't develop lung cancer?</p> <p>21 A. Correct.</p> <p>22 Q. And there are individuals that</p> <p>23 are exposed to chimney smoke and they don't</p> <p>24 develop cancer, testicular cancer, correct?</p> <p>25 A. Well, I assume you meant soot,</p>



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<p style="text-align: right;">Page 130</p> <p>1 but I'll -- assuming you agree with my 2 assumption as to your question, I would say 3 correct. 4 Q. In fact, 1975, Sir Percival 5 Pott first reported on the association 6 between kidney -- chimney soot and testicular 7 cancer, correct? 8 MS. MILLER: Objection. 9 THE WITNESS: No, he'd been 10 dead for 200 years in 1975. 11 QUESTIONS BY MR. RESTAINO: 12 Q. Okay. Regardless of his death, 13 do you recall Dr. Pott reporting on the 14 incidence of testicular cancer in chimney 15 sweeps? 16 MS. MILLER: Objection. 17 THE WITNESS: I recall Sir 18 Percival Pott reporting on an 19 association between scrotal cancer and 20 sweeping chimney -- chimneys. 21 QUESTIONS BY MR. RESTAINO: 22 Q. In fact, that may have been the 23 first reported association between an 24 environmental factor and the development of 25 cancer, agreed?</p>	<p style="text-align: right;">Page 132</p> <p>1 QUESTIONS BY MR. RESTAINO: 2 Q. You would agree, though, that 3 certain genes, such as BRCA1, BRCA2, can give 4 women an inherent susceptibility to breast 5 cancer, correct? 6 A. Inherent -- if we substitute 7 "inherit" for "inherent," I would agree with 8 that statement, yes. 9 MS. MILLER: I was about to 10 object to that word. You didn't give 11 me a chance. 12 THE WITNESS: Noted. 13 MS. MILLER: Did you mean 14 inherited, or did you mean inherent? 15 MR. RESTAINO: It's written 16 "inherited," and I think I misspoke. 17 MS. MILLER: Okay. 18 MR. RESTAINO: So I'll repeat 19 the question. 20 MS. MILLER: I didn't know what 21 you meant by "inherent," so -- 22 THE WITNESS: I know what you 23 meant, and so I'll -- 24 QUESTIONS BY MR. RESTAINO: 25 Q. Answer with the understanding</p>
<p style="text-align: right;">Page 131</p> <p>1 MS. MILLER: Objection. 2 THE WITNESS: No, I think 3 that's probably a reach. I think that 4 was an extraordinarily strong 5 association between an environmental 6 exposure and the development of a 7 cancer. 8 To the extent that it was the 9 first report, I really couldn't say. 10 QUESTIONS BY MR. RESTAINO: 11 Q. Okay. As you sit here today, 12 can you think of a prior environmental 13 exposure report leading to increased risk of 14 cancer in people? 15 A. Prior to the 18th century? 16 Q. Yes. 17 A. No. 18 Q. Well, would you agree -- or do 19 you have an opinion to a reasonable degree of 20 medical certainty or scientific certainty as 21 to what percentage of cancer in this country 22 are related to environmental factors? 23 MS. MILLER: Objection. 24 THE WITNESS: No. 25</p>	<p style="text-align: right;">Page 133</p> <p>1 it was inherited? 2 A. Correct. 3 Q. And in fact, the inherited 4 mutations in BRCA1, BRCA2 also confer a 5 predisposition to ovarian cancer in some 6 women, correct? 7 A. That's correct. 8 Q. But not everyone who has the 9 BRCA1 and BRCA2 mutation develops breast 10 cancer or ovarian cancer, correct? 11 A. Correct. 12 Q. Would you agree or disagree 13 that the general consensus of the medical 14 community is that many cancers are 15 environmentally caused? 16 A. I would disagree. There's 17 absolutely no evidence to support that 18 statement as you read it, today as we sit 19 here. 20 Q. Today has it changed, in your 21 opinion? 22 A. Yes, I think it has. 23 Q. And when do you think it 24 changed? 25 A. I think it changed dramatically</p>

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<p style="text-align: right;">Page 134</p> <p>1 in the late 1970s when Bishop and Varmus made</p> <p>2 their seminal observation that human beings</p> <p>3 had, within their genome, cells that in a</p> <p>4 retroviral-induced context caused cancer in</p> <p>5 chickens, leading to the ultimate realization</p> <p>6 that cancer in humans is a result of</p> <p>7 mutations in genes within the cells of our</p> <p>8 various organs and tissues.</p> <p>9 Q. Okay.</p> <p>10 A. Prior to 1978 when those</p> <p>11 seminal publications were published, we spent</p> <p>12 a lot of time looking for links between the</p> <p>13 environment and cancer, a lot of time looking</p> <p>14 for links between viruses and cancer.</p> <p>15 We -- in a very general sense</p> <p>16 "we," the field -- spent a lot of time</p> <p>17 looking for anything that could explain</p> <p>18 cancer pathogenesis. And that was really a</p> <p>19 transformational event, a true inflection</p> <p>20 point in our understanding of cancer</p> <p>21 pathogenesis in humans generally, the</p> <p>22 understanding that the aberrant regulation or</p> <p>23 mutation of cells in one or another tissue</p> <p>24 was in fact the driving force of cancer</p> <p>25 development in most cases of cancer. There</p>	<p style="text-align: right;">Page 136</p> <p>1 Do you see that, sir?</p> <p>2 A. Cancer Causality and Etiology,</p> <p>3 yes.</p> <p>4 Q. And then underneath that, you,</p> <p>5 Dr. Huff and Dr. Barrett write, "Identifiable</p> <p>6 causes of most human cancers unfortunately</p> <p>7 remain unknown, yet the general consensus</p> <p>8 appears to be that many are, quote,</p> <p>9 environmentally caused and hence should be</p> <p>10 preventable."</p> <p>11 Did I read that correctly?</p> <p>12 A. You read it correctly.</p> <p>13 Q. And that was published by</p> <p>14 Drs. Huff, yourself and Barrett in "Cellular</p> <p>15 and Molecular Mechanisms of Hormonal</p> <p>16 Carcinogenesis: Environmental Influences,"</p> <p>17 1996; is that correct?</p> <p>18 A. Yes. 20, 30 years ago.</p> <p>19 Q. And in the next paragraph you</p> <p>20 wrote, "Known causes of cancer include both</p> <p>21 external factors, open paren, tobacco smoke,</p> <p>22 chemicals, occupational exposure</p> <p>23 circumstances, radiation, viruses, close</p> <p>24 paren, and internal factors, open paren,</p> <p>25 hormones, immune conditions, inherited genes,</p>
<p style="text-align: right;">Page 135</p> <p>1 are exceptions, of course.</p> <p>2 Q. And this was prior to 1978?</p> <p>3 A. No, the inflection point was</p> <p>4 1978, and I was talking about subsequent.</p> <p>5 Q. Okay.</p> <p>6 A. Following 1978 where the whole</p> <p>7 notion of cancer genes took root, catalyzed,</p> <p>8 again, a virtual transformational period</p> <p>9 involving our understanding of the driving</p> <p>10 force of cancer development.</p> <p>11 Q. If you would turn again to I</p> <p>12 think it's the last exhibit, which is 6, the</p> <p>13 paper by James Huff and yourself and Carl</p> <p>14 Barrett, and turn to page 11?</p> <p>15 A. This is Exhibit 5, correct?</p> <p>16 No. I'm sorry, I'm on my --</p> <p>17 Q. I think it's 6.</p> <p>18 A. Exhibit 6, you're correct. I</p> <p>19 had my --</p> <p>20 Q. That's quite all right.</p> <p>21 A. -- expert report.</p> <p>22 Q. There's a section there called</p> <p>23 Cancer Causality and Etiology.</p> <p>24 A. Which page, please?</p> <p>25 Q. Page 11.</p>	<p style="text-align: right;">Page 137</p> <p>1 close paren, as well as aging," which we</p> <p>2 discussed earlier, correct?</p> <p>3 MS. MILLER: Is there a</p> <p>4 question there?</p> <p>5 QUESTIONS BY MR. RESTAINO:</p> <p>6 Q. Did I read that correctly?</p> <p>7 A. You read it correctly.</p> <p>8 MS. MILLER: Except to that</p> <p>9 which we had discussed earlier.</p> <p>10 That's not in here.</p> <p>11 QUESTIONS BY MR. RESTAINO:</p> <p>12 Q. Now, Doctor, a moment ago or</p> <p>13 some time ago, I did -- I asked you about the</p> <p>14 concept of multifactorial disease.</p> <p>15 Do you recall that?</p> <p>16 A. I do.</p> <p>17 Q. Would you agree that there are</p> <p>18 multiple biologically plausible risk factors</p> <p>19 for the development of ovarian cancer?</p> <p>20 MS. MILLER: Objection.</p> <p>21 I think the witness testified</p> <p>22 earlier that he doesn't think</p> <p>23 biologically plausible is -- I just</p> <p>24 want to get exactly right what he</p> <p>25 said.</p>

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<p style="text-align: right;">Page 138</p> <p>1 THE WITNESS: I can answer it 2 again. 3 MS. MILLER: Okay. 4 THE WITNESS: I don't equate 5 association with causality. 6 QUESTIONS BY MR. RESTAINO: 7 Q. Okay. Would you agree that 8 there are risk factors that are associated 9 with an increased risk for the development of 10 ovarian cancer? 11 A. Yes. 12 Q. Would that include, stating the 13 obvious, gender? 14 A. Yes. 15 Q. Age over 45? 16 A. Yes. 17 Q. How about a woman who has not 18 had a tubal ligation, does that increase the 19 risk? 20 A. I wouldn't phrase it that way, 21 no. 22 Q. How would you phrase it? 23 A. I would say that tubal ligation 24 decreases the risk. 25 Q. Okay. How about no</p>	<p style="text-align: right;">Page 140</p> <p>1 A. Nulliparity is a risk factor 2 for ovarian cancer. 3 Q. Would no oral contraceptive use 4 be a risk factor for the development of 5 ovarian cancer? 6 MS. MILLER: Objection. 7 THE WITNESS: I disagree with 8 the statement. 9 QUESTIONS BY MR. RESTAINO: 10 Q. Is a positive family history of 11 ovarian cancer a risk factor for the 12 development of ovarian cancer? 13 A. I would suggest that a family 14 history involving first degree-relatives is a 15 risk factor for the development of ovarian 16 cancer. 17 Q. Would you agree that a woman 18 who has early onset breast cancer is at 19 increased risk for the development of ovarian 20 cancer? 21 MS. MILLER: Objection. 22 THE WITNESS: Yes, but I'd like 23 to qualify my answers to all of these 24 questions with respect to the 25 magnitude of risk, because it differs</p>
<p style="text-align: right;">Page 139</p> <p>1 breastfeeding, would that be a risk or a 2 protective factor? 3 MS. MILLER: Objection. 4 THE WITNESS: Well, to the 5 extent that parity reduces risk and 6 breast cancer -- or breast -- I'm 7 sorry, breastfeeding is almost always 8 associated with having children, I 9 would agree that breastfeeding is 10 associated with a reduced risk of 11 developing ovarian cancer. 12 QUESTIONS BY MR. RESTAINO: 13 Q. And the flip side, would no 14 breastfeeding, no live births, be a risk 15 factor for the development of ovarian cancer? 16 MS. MILLER: Objection. 17 THE WITNESS: I -- live births? 18 That's a little confusing to me. 19 QUESTIONS BY MR. RESTAINO: 20 Q. Full-term delivery of a baby. 21 A. We're going to have to start 22 over with the question. I'm sorry. 23 Q. Do you believe that no -- that 24 with no live births would be a risk factor 25 for the development of ovarian cancer?</p>	<p style="text-align: right;">Page 141</p> <p>1 with all of the risk factors that 2 we've just articulated over a period 3 of -- 4 QUESTIONS BY MR. RESTAINO: 5 Q. And I apologize. I should have 6 said this at the outset. 7 During the deposition I get to 8 ask my questions, and sometimes it's a yes or 9 no, disagree or agree answer. 10 At the end of the deposition, 11 the attorneys representing Johnson &amp; Johnson 12 get to also ask you questions. So if there 13 are questions that you want -- answers you 14 want to expand upon, you will have time to do 15 that at the end of the deposition. 16 MS. MILLER: I think he can 17 also expand upon his answers during 18 the deposition in order to give full, 19 complete answers. 20 MR. RESTAINO: Not if the 21 witness is going to come out with 22 "fourscore and seven years ago" like 23 Dr. Shih. We're just not going down 24 that route today. 25 MS. MILLER: I see.</p>

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<p style="text-align: right;">Page 142</p> <p>1 QUESTIONS BY MR. RESTAINO: 2 Q. Doctor, is the use of oral -- 3 A. I'm sorry, perhaps I 4 misunderstood the ground rules. 5 In my mind, an answer is an 6 answer. 7 Q. Yes, I like to go by that, too. 8 So if I ask you if you agree or disagree, 9 it's a simple answer: "agree" or "disagree." 10 If you want to expand upon it, 11 then you'll have your opportunity at the end 12 of the deposition. 13 MS. MILLER: If you do not feel 14 that agree or disagree is a complete 15 and full and honest answer, then you 16 should give a full, complete and 17 honest answer. 18 QUESTIONS BY MR. RESTAINO: 19 Q. Doctor, would you agree that 20 the use of oral contraceptives are a 21 protective factor regarding ovarian cancer? 22 MS. MILLER: Are we talking 23 about all ovarian cancer? Are you 24 just talking about a specific ovarian 25 cancer?</p>	<p style="text-align: right;">Page 144</p> <p>1 of oral contraceptives for five years 2 or more is an especially strong 3 association which differs from the 4 magnitude of many risks that we've 5 previously discussed. 6 QUESTIONS BY MR. RESTAINO: 7 Q. Doctor, sitting here today in 8 2019, in addition to age over 45, no tubal 9 ligation, no breastfeeding, no live births, 10 oral contraceptive use, Jewish ethnicity, 11 family history of ovarian cancer, early onset 12 of breast cancer, would you add long-term 13 genital talcum powder to the list of risk 14 factors for the development of cancer, 15 ovarian cancer? 16 A. No. 17 Q. And why is that? 18 A. It's twofold. At best, the 19 epidemiologic association is quite weak, and 20 no biological plausibility. 21 Q. How are you defining biological 22 plausibility now? 23 MS. MILLER: Objection. 24 THE WITNESS: I define 25 biological plausibility now as I</p>
<p style="text-align: right;">Page 143</p> <p>1 I just want to make sure we're 2 all on the same page here. 3 MR. RESTAINO: Ovarian cancer 4 as in -- we're talking about in this 5 litigation and what's been discussed 6 in Dr. Saed's report and the 7 biological plausibility of plaintiff 8 experts referring to ovarian cancer. 9 QUESTIONS BY MR. RESTAINO: 10 Q. Would the use of oral 11 contraceptive be considered a protective 12 factor? 13 A. Would you like to finish the 14 question? 15 Q. Would the use of oral 16 contraceptives be considered a protective 17 factor for the development of ovarian cancer? 18 MS. MILLER: Objection. 19 THE WITNESS: The use of oral 20 contraceptives confers a decreased 21 risk of developing epithelial ovarian 22 carcinoma, including all its 23 histologic variants. 24 And I might add that the 25 decreased risk associated with the use</p>	<p style="text-align: right;">Page 145</p> <p>1 define it always, which is in essence 2 the articulation of a cogent mechanism 3 that gets you from a weak association 4 to causality. 5 QUESTIONS BY MR. RESTAINO: 6 Q. How do you define a cogent? 7 A. I think a cogent mechanism, it 8 needs to be clear as opposed to muddled, I 9 think it needs to be logical as opposed to 10 illogical, and I think it needs to be 11 compelling as opposed to speculative. 12 Q. Can it be possible? 13 A. Can what be possible? 14 MS. MILLER: Objection. 15 QUESTIONS BY MR. RESTAINO: 16 Q. A cogent biological 17 plausibility. 18 A. I'm sorry, sir, I've lost you 19 completely. 20 Q. Using the word "cogent" for 21 biological plausibility, can that be a 22 possible cause or risk factor? 23 A. I'm sorry, I just can't begin 24 to interpret your question. 25 Q. What part of it can't you</p>

37 (Pages 142 to 145)

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<p style="text-align: right;">Page 146</p> <p>1 interpret?</p> <p>2 A. The sentence doesn't make sense</p> <p>3 to me.</p> <p>4 Q. Okay.</p> <p>5 A. The question doesn't make</p> <p>6 sense.</p> <p>7 Q. We've defined cogent as you use</p> <p>8 it, correct?</p> <p>9 Biological plausibility. How</p> <p>10 do you define the English word</p> <p>11 "plausibility"?</p> <p>12 MS. MILLER: Objection. Asked</p> <p>13 and answered.</p> <p>14 THE WITNESS: The same as I</p> <p>15 would define biological plausibility,</p> <p>16 leaving out biological and applying</p> <p>17 plausibility to any other context.</p> <p>18 QUESTIONS BY MR. RESTAINO:</p> <p>19 Q. So if the -- if the dictionary</p> <p>20 defines plausibility as possible, and we add</p> <p>21 biological in front of it, as you just put,</p> <p>22 then we're talking about biological</p> <p>23 possibility, correct?</p> <p>24 MS. MILLER: Objection.</p> <p>25 THE WITNESS: No, I think we're</p>	<p style="text-align: right;">Page 148</p> <p>1 A. You read it correctly.</p> <p>2 Q. And have you performed any</p> <p>3 experiments to rule out talcum powder as one</p> <p>4 of the unknown causes of the somatic genetic</p> <p>5 mutations leading to ovarian cancer?</p> <p>6 MS. MILLER: Objection.</p> <p>7 THE WITNESS: It's impossible</p> <p>8 to perform a negative experiment.</p> <p>9 QUESTIONS BY MR. RESTAINO:</p> <p>10 Q. Have you performed any</p> <p>11 experiments to determine whether talcum</p> <p>12 powder was a cause of any of the somatic</p> <p>13 genetic mutations leading to ovarian cancer?</p> <p>14 A. You'd have to describe the</p> <p>15 context.</p> <p>16 Q. The context of this sentence,</p> <p>17 sir.</p> <p>18 "The context of the causes of</p> <p>19 somatic genetic mutations acquired in the</p> <p>20 organ in which a cancer ultimately develops</p> <p>21 remain largely unknown for ovarian cancer and</p> <p>22 most other cancers."</p> <p>23 In attempt to learn the</p> <p>24 unknown, have you -- have you attempted any</p> <p>25 experiments utilizing talcum powder and see</p>
<p style="text-align: right;">Page 147</p> <p>1 playing word games, and I just -- I</p> <p>2 just can't -- I'm not going to play</p> <p>3 syntax games with you.</p> <p>4 QUESTIONS BY MR. RESTAINO:</p> <p>5 Q. I'm just trying to ascertain or</p> <p>6 learn your definition so that as the day goes</p> <p>7 on I can use your definitions and words.</p> <p>8 A. And I'm quite confident that I</p> <p>9 offered my best definition for biological</p> <p>10 plausibility at least once, perhaps twice.</p> <p>11 Q. Okay. If you turn now to</p> <p>12 page 3 of your expert report and to the top</p> <p>13 paragraph, approximately eight lines down</p> <p>14 there's a sentence that you write that starts</p> <p>15 on the left with, "The causes of these</p> <p>16 somatic genetic mutations."</p> <p>17 Just let me know when you find</p> <p>18 that, sir.</p> <p>19 A. I've found it.</p> <p>20 Q. "The causes of these, quote,</p> <p>21 somatic, end quote, genetic mutations</p> <p>22 acquired in the organ in which a cancer</p> <p>23 ultimately develops remain largely unknown</p> <p>24 for ovarian cancer and most other cancers."</p> <p>25 Did I read that correctly?</p>	<p style="text-align: right;">Page 149</p> <p>1 the effect on somatic genetic mutations</p> <p>2 leading to ovarian cancer?</p> <p>3 MS. MILLER: Objection.</p> <p>4 THE WITNESS: I'll give it a</p> <p>5 shot.</p> <p>6 I used the word "organ" in the</p> <p>7 sentence, so I have to assume I was</p> <p>8 talking about animals or humans as</p> <p>9 opposed to, for example, cells.</p> <p>10 And I can state unequivocally</p> <p>11 that I've never treated animals or</p> <p>12 humans with talcum powder in order to</p> <p>13 see what might happen.</p> <p>14 QUESTIONS BY MR. RESTAINO:</p> <p>15 Q. Several sentences down, the</p> <p>16 same paragraph on the right-hand side --</p> <p>17 actually, it's one, two, three -- seven lines</p> <p>18 up from the bottom, approximately, there's a</p> <p>19 sentence that starts on the far right with</p> <p>20 "possible mutagenic."</p> <p>21 Do you see that, sir?</p> <p>22 A. Uh-huh, yes.</p> <p>23 Q. "Possible mutagenic mechanisms</p> <p>24 in ovarian and other cancer types include</p> <p>25 unknown environmental exposures and pure</p>



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<p style="text-align: right;">Page 150</p> <p>1 chance."</p> <p>2 Did I read that correctly?</p> <p>3 A. You read it correctly.</p> <p>4 Q. Is it your opinion at this time</p> <p>5 that the possible mutagenic mechanisms in</p> <p>6 ovarian and other cancer types, including</p> <p>7 unknown -- include unknown environmental</p> <p>8 exposures, but you're not willing at this</p> <p>9 time to access -- access -- accept the</p> <p>10 possibility of talcum powder being one of</p> <p>11 those environmental factors?</p> <p>12 MS. MILLER: Objection.</p> <p>13 Is this sentence -- is the</p> <p>14 question over?</p> <p>15 MR. RESTAINO: The question is</p> <p>16 over.</p> <p>17 MS. MILLER: All right.</p> <p>18 Objection.</p> <p>19 THE WITNESS: Well, here, my</p> <p>20 goal in writing this sentence was to</p> <p>21 refer to all cancer types, and so I</p> <p>22 was trying to make that transition</p> <p>23 from ovarian to all cancer types.</p> <p>24 QUESTIONS BY MR. RESTAINO:</p> <p>25 Q. Well --</p>	<p style="text-align: right;">Page 152</p> <p>1 genetic alterations in both oncogenes and</p> <p>2 tumor suppressor genes for their development.</p> <p>3 That is the transformation of a completely</p> <p>4 normal cell into a completely malignant cell</p> <p>5 capable of metastasizing.</p> <p>6 So I'm now speaking broadly</p> <p>7 about all cancers, widely accepted as a</p> <p>8 paradigm in the dictionary sense of what a</p> <p>9 paradigm is. And my goal here was to say in</p> <p>10 some cases -- let's pick a cancer, cervical</p> <p>11 cancer, where HPV infection is recognized as</p> <p>12 a causal factor.</p> <p>13 The reason we recognize it as a</p> <p>14 causal factor is we know that the human</p> <p>15 papilloma virus contains two transforming</p> <p>16 proteins known as E6 and E7. E6 binds to and</p> <p>17 activates the TP53 protein. E7 binds to and</p> <p>18 activates the RB1 tumor suppressor protein.</p> <p>19 And to the extent that the p53</p> <p>20 gene, when active, protects against the</p> <p>21 accumulation of spontaneous genetic damage,</p> <p>22 and RB1, when it's functioning normally,</p> <p>23 prevents inappropriate cell proliferation,</p> <p>24 the loss of constraints on cell proliferation</p> <p>25 and the loss of the so-called guardian of the</p>
<p style="text-align: right;">Page 151</p> <p>1 A. The --</p> <p>2 Q. I'm sorry.</p> <p>3 A. The paragraph is rather -- is</p> <p>4 rather a narrative of the, as we sit here</p> <p>5 today, commonly accepted essence of cancer</p> <p>6 development, which is the acquisition and</p> <p>7 accumulation of genetic mutations in</p> <p>8 oncogenes and tumor suppressor genes,</p> <p>9 regardless of the cancer type, ovarian and</p> <p>10 others. And in some cancer types, we have a</p> <p>11 pretty good idea of what the causes of those</p> <p>12 mutations are.</p> <p>13 In a, quote/unquote, hereditary</p> <p>14 context, the first rate-limiting genetic</p> <p>15 alteration is the mutant gene inherited from</p> <p>16 mom or dad.</p> <p>17 The subsequent genetic</p> <p>18 alterations are acquired -- the subsequent</p> <p>19 necessary genetic alterations are acquired</p> <p>20 somatically, getting back to your question of</p> <p>21 why don't all women with the BRCA1 or 2</p> <p>22 mutation develop breast or ovarian cancer.</p> <p>23 The one genetic mutation is insufficient for</p> <p>24 the development of cancer.</p> <p>25 All cancers require multiple</p>	<p style="text-align: right;">Page 153</p> <p>1 genome p53 lead to subsequent mutations,</p> <p>2 requisite, as I indicated, for all cancers.</p> <p>3 And that's a very good example</p> <p>4 of knowing how a particular exogenous agent</p> <p>5 is both highly associated, indeed 100 percent</p> <p>6 associated, with all squamous carcinomas of</p> <p>7 the cervix and indeed causal based on a deep</p> <p>8 knowledge of the biological mechanism.</p> <p>9 We don't know as much about</p> <p>10 many other cancers as we do about cervical</p> <p>11 cancer. And that's the point I was trying to</p> <p>12 make with this paragraph.</p> <p>13 Q. We're going to return to the</p> <p>14 HPV virus and cancer.</p> <p>15 Suffice to say right now that</p> <p>16 there are many versions of HPV virus,</p> <p>17 correct? Many?</p> <p>18 A. Many isoforms? Isotypes?</p> <p>19 Q. Yes.</p> <p>20 A. Yes, and two are particularly</p> <p>21 carcinogenic.</p> <p>22 Q. And some are not?</p> <p>23 A. Well --</p> <p>24 Q. But we will return to that in a</p> <p>25 moment.</p>



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<p style="text-align: right;">Page 154</p> <p>1 A. I'll grant you that.</p> <p>2 MS. MILLER: Is that a</p> <p>3 question? I mean, is that a question,</p> <p>4 or is that just a statement?</p> <p>5 THE WITNESS: I think it was</p> <p>6 a --</p> <p>7 MS. MILLER: Let's only answer</p> <p>8 questions, not statements.</p> <p>9 QUESTIONS BY MR. RESTAINO:</p> <p>10 Q. What you wrote here, sir, was</p> <p>11 "possible mutagenic mechanisms in ovarian and</p> <p>12 other cancer types include unknown</p> <p>13 environmental exposures and pure chance."</p> <p>14 My question to you is: Of the</p> <p>15 possible mutagenic mechanisms in ovarian</p> <p>16 cancer, including unknown environmental</p> <p>17 exposures, you are not willing at this time</p> <p>18 to accept the possibility of talcum powder</p> <p>19 being one of those factors; is that correct?</p> <p>20 A. That's correct.</p> <p>21 MS. MILLER: Objection.</p> <p>22 THE WITNESS: Sorry.</p> <p>23 QUESTIONS BY MR. RESTAINO:</p> <p>24 Q. And then you write, the next</p> <p>25 sentence, "Indeed, one prominent cancer</p>	<p style="text-align: right;">Page 156</p> <p>1 MS. MILLER: Objection.</p> <p>2 THE WITNESS: You read what I</p> <p>3 wrote correctly.</p> <p>4 QUESTIONS BY MR. RESTAINO:</p> <p>5 Q. Okay. And you did not put in</p> <p>6 that paragraph any of the subsequent</p> <p>7 arguments made following the publication of</p> <p>8 Tomasetti, et al., in Nature, did you?</p> <p>9 A. No, I didn't.</p> <p>10 Q. In addition to Tomasetti and</p> <p>11 Vogelstein, did you review article by Martin</p> <p>12 Nowak and -- I'm not even going to pronounce</p> <p>13 this doctor's last name. It's W-a-c-l-a-w --</p> <p>14 Waclaw, perhaps, titled "Genes, Environment,</p> <p>15 and, quote, Bad Luck, end quote," explaining</p> <p>16 cancer risk in a statistical sense, published</p> <p>17 in Science in March 2017?</p> <p>18 A. Perhaps.</p> <p>19 Could you show me the paper,</p> <p>20 please.</p> <p>21 Q. Absolutely, sir. I'm marking</p> <p>22 it now as Boyd 7.</p> <p>23 (Boyd Exhibit 7 marked for</p> <p>24 identification.)</p> <p>25</p>
<p style="text-align: right;">Page 155</p> <p>1 molecular geneticist recently posited that</p> <p>2 most cancer cases may simply be attributable</p> <p>3 to bad luck, hyphen, genetic mutations</p> <p>4 resulting from chance, errors, in the</p> <p>5 ordinary replication of the cellular genome,</p> <p>6 open paren, 3.3 billion base pairs per cell,</p> <p>7 close paren, whenever one cell divides into</p> <p>8 two. Reference number 4."</p> <p>9 Did I read that correctly?</p> <p>10 A. You read it correctly.</p> <p>11 Q. And how do you define bad luck?</p> <p>12 A. It was an unfortunate term, and</p> <p>13 Dr. Vogelstein received a lot of criticism</p> <p>14 for his use of the term "bad luck."</p> <p>15 But I think he would have been</p> <p>16 better served having used the term</p> <p>17 "stochastic."</p> <p>18 Q. But, sir, in your expert report</p> <p>19 you don't say that it's an unfortunate term,</p> <p>20 nor do you say that you received controversy.</p> <p>21 What you do say is one</p> <p>22 prominent cancer molecular geneticist</p> <p>23 recently posited that most cancer cases may</p> <p>24 simply be attributable to bad luck; isn't</p> <p>25 that correct?</p>	<p style="text-align: right;">Page 157</p> <p>1 QUESTIONS BY MR. RESTAINO:</p> <p>2 Q. And as you see in the far lower</p> <p>3 right-hand corner, this is published in</p> <p>4 Science.</p> <p>5 Would you agree that Science is</p> <p>6 a highly rated scientific journal?</p> <p>7 MS. MILLER: Objection.</p> <p>8 THE WITNESS: I don't rate</p> <p>9 scientific journals. I rate the</p> <p>10 science in the journals.</p> <p>11 QUESTIONS BY MR. RESTAINO:</p> <p>12 Q. First paragraph, Drs. Nowak and</p> <p>13 Waclaw write, "It is a human trait to search</p> <p>14 for explanations for catastrophic events and</p> <p>15 rule out mere, quote, chance, end quote, or,</p> <p>16 quote, bad luck, end quote, when it comes to</p> <p>17 human cancer, but the issue of natural causes</p> <p>18 versus bad luck was raised by Tomasetti and</p> <p>19 Vogelstein about two years ago, open paren</p> <p>20 number 1. Their study, which was widely</p> <p>21 misinterpreted as saying that most cancers</p> <p>22 are due neither to genetic inheritance nor</p> <p>23 environmental factors but simply bad luck</p> <p>24 sparked controversy."</p> <p>25 Did I read that correctly?</p>

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<p style="text-align: right;">Page 158</p> <p>1 A. You read it correctly.</p> <p>2 Q. Would you agree the Tomasetti</p> <p>3 and Vogelstein paper, when it was published,</p> <p>4 sparked controversy?</p> <p>5 A. My memory is that the use of</p> <p>6 the term "bad luck" sparked controversy.</p> <p>7 That was the essence of the uproar.</p> <p>8 Q. Would you agree controversy, in</p> <p>9 essence, means two or more differing</p> <p>10 viewpoints?</p> <p>11 A. That totally depends on the</p> <p>12 context.</p> <p>13 Q. In this context, would you</p> <p>14 agree there was a controversy as to whether</p> <p>15 there was bad luck involved or not bad luck</p> <p>16 involved?</p> <p>17 MS. MILLER: Objection. Vague.</p> <p>18 THE WITNESS: As I indicated</p> <p>19 earlier, it's my memory that the</p> <p>20 controversy in this particular case</p> <p>21 had to do with syntax. Both the</p> <p>22 scientific community and the public</p> <p>23 community were uncomfortable with the</p> <p>24 use of the term "bad luck."</p> <p>25</p>	<p style="text-align: right;">Page 160</p> <p>1 today, the underlying essence of</p> <p>2 cancer pathogenicity, generally</p> <p>3 speaking, which is an extraordinarily</p> <p>4 challenging task in one paragraph.</p> <p>5 And so, yes, there are</p> <p>6 textbooks -- and I'm holding my</p> <p>7 fingers approximately six inches</p> <p>8 apart -- having to do with the</p> <p>9 pathogenicity of human cancer. And so</p> <p>10 in attempting to distill the knowledge</p> <p>11 that the scientific and medical</p> <p>12 communities hold today regarding the</p> <p>13 pathogenicity of human cancer</p> <p>14 generally, I did indeed leave out a</p> <p>15 lot.</p> <p>16 QUESTIONS BY MR. RESTAINO:</p> <p>17 Q. It was not your intention to</p> <p>18 distill to the judge that may have been</p> <p>19 reading your expert report that some women</p> <p>20 develop ovarian cancer strictly through bad</p> <p>21 luck, was it?</p> <p>22 MS. MILLER: Objection.</p> <p>23 THE WITNESS: It was my</p> <p>24 intention to explain to whoever may</p> <p>25 read this expert report that one</p>
<p style="text-align: right;">Page 159</p> <p>1 QUESTIONS BY MR. RESTAINO:</p> <p>2 Q. And that's the totality of your</p> <p>3 understanding of the controversy?</p> <p>4 A. Yes, it is.</p> <p>5 Q. You don't discuss the</p> <p>6 controversy in your expert report when</p> <p>7 stating that one prominent molecular</p> <p>8 geneticist published on bad luck, do you?</p> <p>9 MS. MILLER: Objection. Asked</p> <p>10 and answered.</p> <p>11 QUESTIONS BY MR. RESTAINO:</p> <p>12 Q. Do you?</p> <p>13 A. No. And I would only add that</p> <p>14 there are many things that I don't state in</p> <p>15 my expert report.</p> <p>16 Q. Somewhere in your -- I'm sorry.</p> <p>17 Somewhere in your expert</p> <p>18 report --</p> <p>19 MS. MILLER: I think he was in</p> <p>20 the middle of a sentence.</p> <p>21 MR. RESTAINO: I'm sorry, I</p> <p>22 thought I heard a period.</p> <p>23 THE WITNESS: You know, again,</p> <p>24 the purpose of this paragraph was an</p> <p>25 attempt to distill, as we sit here</p>	<p style="text-align: right;">Page 161</p> <p>1 hypothesis regarding the cause of the</p> <p>2 requisite genetic mutations and</p> <p>3 cancers generally may be stochastic</p> <p>4 errors in DNA replication during the</p> <p>5 process of normal cell division.</p> <p>6 QUESTIONS BY MR. RESTAINO:</p> <p>7 Q. Maybe equate to possibility?</p> <p>8 MS. MILLER: Objection.</p> <p>9 THE WITNESS: Well, if we're</p> <p>10 going -- again, could you read back my</p> <p>11 answer, please, and see what he's</p> <p>12 equating to what?</p> <p>13 I would like my answer to stand</p> <p>14 as I -- you're asking me to redefine a</p> <p>15 term I used in answering your</p> <p>16 question, and I would prefer not to</p> <p>17 redefine terms that I've used in</p> <p>18 answering your question.</p> <p>19 QUESTIONS BY MR. RESTAINO:</p> <p>20 Q. Well, when you say that it may</p> <p>21 be somatically particular errors in DNA</p> <p>22 replication -- and I'm just asking there,</p> <p>23 inasmuch as you used the word "may" -- does</p> <p>24 that equate to possibly?</p> <p>25 MS. MILLER: Objection.</p>

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<p style="text-align: right;">Page 162</p> <p>1 THE WITNESS: We're actually</p> <p>2 debating as to whether "may" is</p> <p>3 synonymous with "possibly"?</p> <p>4 QUESTIONS BY MR. RESTAINO:</p> <p>5 Q. How would you use may? With</p> <p>6 probable? Certainly?</p> <p>7 MS. MILLER: Objection.</p> <p>8 QUESTIONS BY MR. RESTAINO:</p> <p>9 Q. I'm just trying to use your</p> <p>10 words.</p> <p>11 MS. MILLER: Objection. He</p> <p>12 gave his words.</p> <p>13 THE WITNESS: I gave you my</p> <p>14 words.</p> <p>15 (Boyd Exhibit 8 marked for</p> <p>16 identification.)</p> <p>17 QUESTIONS BY MR. RESTAINO:</p> <p>18 Q. May. Okay.</p> <p>19 Let's turn to a paper that</p> <p>20 we've now marked and handed to you titled</p> <p>21 "Substantial Contribution of Extrinsic Risk</p> <p>22 Factors to Cancer Development," lead author</p> <p>23 Song Wu, W-u, published in Nature in June</p> <p>24 of 2016.</p> <p>25 Do you have that, sir?</p>	<p style="text-align: right;">Page 164</p> <p>1 percent, close paren, to cancer development.</p> <p>2 First, we demonstrate that the correlation</p> <p>3 between stem-cell division and cancer risk</p> <p>4 does not distinguish between the effects of</p> <p>5 intrinsic and extrinsic factors. Next, we</p> <p>6 show that intrinsic risk is better estimated</p> <p>7 by the lower bound risk controlling for total</p> <p>8 stem cell divisions. Finally, we show that</p> <p>9 the rates of endogenous mutation accumulation</p> <p>10 by intrinsic processes are not sufficient to</p> <p>11 account for the observed cancer risk.</p> <p>12 Collectively, we conclude that cancer risk is</p> <p>13 heavily influenced by intrinsic factors.</p> <p>14 These results may carry immense consequences</p> <p>15 for strategizing cancer prevention, research</p> <p>16 and public health."</p> <p>17 Did I read that correctly?</p> <p>18 A. You read it correctly.</p> <p>19 Q. Now, Doctor, safe to say that</p> <p>20 you did not reference this paper by Wu, et</p> <p>21 al., in your expert report, correctly --</p> <p>22 correct?</p> <p>23 MS. MILLER: Objection.</p> <p>24 THE WITNESS: You are correct</p> <p>25 that I did not reference this article.</p>
<p style="text-align: right;">Page 163</p> <p>1 A. I just want to make sure that</p> <p>2 Ms. Miller has a copy and that I have a</p> <p>3 copy --</p> <p>4 MS. MILLER: I do. We both</p> <p>5 have copies.</p> <p>6 THE WITNESS: -- and that we're</p> <p>7 not taking each other's copies.</p> <p>8 MS. MILLER: I'm not going to</p> <p>9 steal your copy, I promise.</p> <p>10 THE WITNESS: I believe your</p> <p>11 question was, do I have that paper.</p> <p>12 Yes, I do.</p> <p>13 QUESTIONS BY MR. RESTAINO:</p> <p>14 Q. And if you take a look at the</p> <p>15 summary written on the first page, "Recent</p> <p>16 research has highlighted a strong correlation</p> <p>17 between tissue-specific cancer risk and the</p> <p>18 lifetime number of tissue-specific stem cell</p> <p>19 divisions. Whether such correlation implies</p> <p>20 a high, unavoidable, intrinsic cancer risk</p> <p>21 has become a key public health debate with</p> <p>22 dissemination of the, quote -- or bad luck,</p> <p>23 quote, hypothesis. Here, we provide evidence</p> <p>24 that intrinsic risk factors contribute only</p> <p>25 modestly, open paren, less than 10 to 30</p>	<p style="text-align: right;">Page 165</p> <p>1 QUESTIONS BY MR. RESTAINO:</p> <p>2 Q. And if you turn to page 2, sir,</p> <p>3 the top paragraph, the first full sentence</p> <p>4 after references numbers 6 and 7, "Much</p> <p>5 discussion has been made."</p> <p>6 Do you see where I am, sir?</p> <p>7 A. Yes.</p> <p>8 Q. "Much discussion has been made</p> <p>9 to argue against the bad luck hypothesis,</p> <p>10 references 5 to 13, yet none offered specific</p> <p>11 alternatives to quantifiably evaluate the</p> <p>12 contribution of extrinsic risk factors in</p> <p>13 cancer development. Applying several</p> <p>14 distinct modeling approaches, we here provide</p> <p>15 strong evidence that unavoidable, intrinsic</p> <p>16 risk factors contribute only modestly, open</p> <p>17 paren, less than 10 to approximately 20,</p> <p>18 30 percent, close paren, to the development</p> <p>19 of many common cancers."</p> <p>20 Did I read that correctly?</p> <p>21 A. You did.</p> <p>22 Q. So, Doctor, other than writing</p> <p>23 "Indeed, one prominent cancer molecular</p> <p>24 geneticist recently posited that most cancer</p> <p>25 cases can simply be attributable to bad</p>

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<p>1 luck," you do not provide any references in 2 your expert report regarding follow-up 3 publications which argue against the bad luck 4 hypotheses; is that correct? 5 MS. MILLER: Objection. 6 THE WITNESS: That is correct. 7 And I would add that my purpose 8 in attempting to distill the great 9 body of knowledge that currently 10 exists as we sit here today as to the 11 etiology in general of all cancers in 12 general, I'm sure I left out thousands 13 of, if not hundreds of thousands, of 14 publications. 15 My purpose was to distill a 16 large body of evidence using an 17 example. 18 QUESTIONS BY MR. RESTAINO: 19 Q. Doctor, are you familiar with 20 the term "confirmation bias"? 21 MS. MILLER: Objection. 22 THE WITNESS: That strikes me 23 as an epidemiologic/statistical term, 24 and I'm not prepared to discuss 25 statistical, epidemiologic concepts.</p>	<p>1 housekeeping or do you want to... 2 MR. RESTAINO: Yeah, this is a 3 good time by me. 4 MS. MILLER: Great. 5 THE WITNESS: I'm sorry, are we 6 done with Huff, Boyd and Barrett? 7 MR. RESTAINO: Yes, sir. 8 THE WITNESS: Thank you. 9 VIDEOGRAPHER: Off the record 10 at 12:36 p.m. 11 (Off the record at 12:36 p.m.) 12 VIDEOGRAPHER: We are back on 13 record at 1:10 p.m. 14 QUESTIONS BY MR. RESTAINO: 15 Q. Welcome back, Dr. Boyd. And as 16 we were discussing off the record, however, 17 the same thing applies: If you need or want 18 anytime to take a break, you get to call 19 timeout at any time. 20 A. Thank you. 21 Q. You're welcome. 22 Now, Doctor, I have marked as 23 Exhibit 9 -- we only have a couple copies. 24 MR. RESTAINO: Do you have a -- 25 copies of the e-mails?</p>
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<p>1 QUESTIONS BY MR. RESTAINO: 2 Q. In non-epidemiological, 3 statistical parlance, are you familiar with 4 the concept of cherry-picking papers, studies 5 or articles that support your point of view? 6 A. Cherry-picking is indeed a 7 colloquialism I'm familiar with, and I'm 8 certain you're going to point out where I 9 used it in my expert report. 10 But, yes, I'm familiar with the 11 term. 12 Q. Okay. If you would turn now to 13 your expert report, the bottom of page 3, 14 there's a Section 4 down there. 15 A. Okay. Let's see, we've got -- 16 Q. And, Doctor, I'll withdraw that 17 statement for a moment. I'll just let you 18 know I think we're all done with Wu and 19 Nowak, if you want to get it out of your way, 20 and just keep your expert report -- 21 A. Thank you. 22 Q. -- just for housekeeping 23 purposes. 24 MS. MILLER: Is this a good 25 time to break for lunch if we're</p>	<p>1 MS. MILLER: Uh-huh. 2 QUESTIONS BY MR. RESTAINO: 3 Q. And, Doctor, did you get a 4 chance to look at these e-mails during the 5 lunch break? 6 A. I flipped through them. It was 7 a large stack, but, yes, I had a chance to 8 look at them. 9 Q. Do they refresh your memory at 10 all regarding e-mail, telephone and physical 11 meetings with Dr. Emmel and another attorney 12 in or about March of 2017? 13 A. It refreshes my memory about 14 e-mails and a telephone conversation with a 15 female attorney and possibly someone else, 16 but, I'm sorry, I have absolutely no 17 recollection of a face-to-face meeting. 18 (Boyd Exhibit 9 marked for 19 identification.) 20 QUESTIONS BY MR. RESTAINO: 21 Q. Okay. Do you have any 22 recollection whatsoever of a telephonic 23 communication? 24 A. Yes. 25 Q. And do you recall at that time</p>

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<p style="text-align: right;">Page 170</p> <p>1 sharing with Dr. Emmel and anyone else who 2 might have been on the phone your opinion 3 regarding the biological plausibility of 4 talcum powder and ovarian cancer? 5 A. Not specifically. I can only 6 presume in my strongest, albeit vague, memory 7 of the discourse was that I wasn't their guy. 8 Q. Did you -- 9 A. After I understood which side 10 of the argument plaintiffs' attorneys were 11 on. And I think that was a mutual agreement 12 between presumably the woman to your right 13 and myself. 14 Q. Okay. I have marked these 15 e-mails as 9, and I'll just put them here for 16 the court reporter. 17 One other thing which I should 18 have said in the beginning, and it always 19 makes for fun at the end of the deposition: 20 The documents with the orange sticker on them 21 have to go with him, so we can't take our 22 copies. So if you have some in a pile, let's 23 be careful with them. 24 Okay? 25 A. I'm sorry. Him? Her?</p>	<p style="text-align: right;">Page 172</p> <p>1 I read that correctly? 2 A. Both. 3 Q. Thank you. 4 Yet when I asked you earlier 5 about your keywords that you utilized in 6 conducting your search of the biomedical 7 literature for your report, you didn't 8 include inflammation in those -- that list of 9 keywords; is that correct? 10 A. Yes, but I modified my answer 11 to that question by explaining that I did get 12 around to looking at papers relating 13 inflammation to -- ostensibly to talc 14 exposure and ovarian cancer by virtue of 15 having read thoroughly the various documents 16 that we've discussed multiple times now 17 relating to Dr. Saed, his paper, his 18 deposition, his expert report and so forth. 19 Q. Okay. Well, now, Doctor, I'm 20 just going to ask you to jump ahead, and then 21 we'll come back down. But if you go to 22 page 18 of your report, and on the final 23 paragraph you start off with, "Finally, 24 Dr. Saed." 25 Do you see that, sir, the last</p>
<p style="text-align: right;">Page 171</p> <p>1 Q. Her. 2 A. Her. 3 Q. Yes, I'm sorry. 4 A. You want to leave them out 5 there? 6 Q. Probably safe. We don't need 7 it. 8 A. Okay. 9 Q. Now, if you return to your 10 expert report at the bottom of page 3, 11 there's a Section 4. 12 Do you see that, sir? 13 A. Yes. 14 Q. In the first sentence you 15 write, "Plaintiff experts propose that talc 16 causes inflammation, which leads to cancer, 17 or that inflammation causes oxidative stress, 18 which damages DNA, which results in cancer." 19 And did I read that correctly? 20 A. Yes, you did. 21 Q. And in the next sentence you 22 write, "These explanations are simplistic, 23 speculative and lacks sufficient scientific 24 support to be deemed plausible." 25 Did I read that carefully? Did</p>	<p style="text-align: right;">Page 173</p> <p>1 paragraph? 2 A. Uh-huh. Yes. 3 Q. "Finally, Dr. Saed appears to 4 take for granted that ovarian cancer is 5 caused by inflammation, but this, too, has 6 not been established. Dr. Saed essentially 7 ignores the body of science suggesting that 8 chronic inflammation does not play a role in 9 the development of ovarian, reference 82, as 10 well as studies that considered whether 11 aspirin use and anti-inflammatory drugs 12 reduced the risk of ovarian, reference 83, 13 with mixed results." 14 And did I read that correctly? 15 A. More or less, but I submit that 16 you read it correctly. 17 Q. Okay. Thank you. 18 Now, Doctor, did you ignore the 19 body of science suggesting that chronic 20 inflammation does, in fact, play a role in 21 the development of ovarian cancer? 22 MS. MILLER: Objection. 23 THE WITNESS: I didn't 24 consciously ignore anything. 25</p>

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<p style="text-align: right;">Page 174</p> <p>1 QUESTIONS BY MR. RESTAINO: 2 Q. Well, you ignored the Nowak 3 editorial and the Wu paper that conflicted 4 with your opinion that cancer can be caused 5 by bad luck, did you not? 6 MS. MILLER: Wait a minute. 7 Where does he say he has the opinion 8 that cancer can be caused by bad luck? 9 What are you talking about? 10 That was a sentence that said, 11 "indeed, one scientist." 12 QUESTIONS BY MR. RESTAINO: 13 Q. One prominent geneticist plays 14 into bad luck -- 15 MS. MILLER: Has posited. 16 QUESTIONS BY MR. RESTAINO: 17 Q. And that's what you wrote, 18 correct? 19 A. Could you please ask the 20 question? 21 Q. Well, I'll strike that 22 question. 23 MS. MILLER: Good idea. 24 MR. RESTAINO: The record will 25 stand on itself.</p>	<p style="text-align: right;">Page 176</p> <p>1 would you agree? 2 A. That's -- I would -- I would 3 suggest that if I did a PubMed search, a 4 Googlian search, with ovarian, capital A, 5 capital N, capital D, cancer, there may be 50 6 to a hundred thousand papers that might pop 7 up. 8 Q. So how did you select the ones 9 that you were going to rely upon for your 10 expert report? 11 A. Because it's necessary to parse 12 a hundred thousand papers into those that are 13 particularly relevant to the hypothesis 14 currently being litigated. 15 Q. And did you parse the hundred 16 thousand papers into those that supported 17 your opinions in this regard and were in 18 conflict with your opinions in this regard? 19 MS. MILLER: Objection. 20 THE WITNESS: First of all, 21 100,000 is just an extraordinarily 22 general estimate, but I would be happy 23 to allow any of you to type in 24 "ovarian" and "cancer" and see what 25 comes up in PubMed and we can get to</p>
<p style="text-align: right;">Page 175</p> <p>1 (Boyd Exhibit 10 marked for 2 identification.) 3 QUESTIONS BY MR. RESTAINO: 4 Q. Now, Doctor, I've marked as 5 Boyd 10 a paper titled "C-reactive Protein as 6 Independent Prognostic Variable in Patients 7 with Ovarian Cancer." Lead author is Hefler, 8 H-e-f-l-e-r, published in Clinical Cancer 9 Research, 2008. 10 Have you seen this paper 11 before, Doctor? 12 A. If I have, I don't -- it's all 13 the same. I don't remember seeing it, no. 14 Q. Okay. I'll represent to you 15 that it's not referenced in your expert 16 report. 17 A. Thank you. 18 Q. And, Doctor, the title contains 19 the words "ovarian cancer," correct? 20 A. The title does contain the 21 words "ovarian cancer." 22 Q. So if one was conducting a 23 narrative search of the biomedical literature 24 using keywords "ovarian" and "cancer," then 25 one would expect this paper to come up also;</p>	<p style="text-align: right;">Page 177</p> <p>1 an exact number, but I don't think 2 that's the issue. 3 With respect to your -- the 4 second part of your question, it's my 5 experience as a biomedical researcher 6 over however many years it's been, 35, 7 that papers' titles are more often 8 than not agnostic to the conclusion 9 reached. 10 And so if I'm going to select, 11 based on a PubMed search which 12 includes titles and authors, which 13 papers to read, at the end of the day, 14 it's pretty much a random process. 15 QUESTIONS BY MR. RESTAINO: 16 Q. Well, suffice to say, you did 17 not select this paper to read, correct? 18 A. I don't remember reading it, 19 that is correct. 20 Q. Okay. And if you would look at 21 the abstract, see they write, "Purpose: To 22 evaluate serum C-reactive protein, open 23 paren, CRP, close paren, as prognostic 24 variable in patients with epithelial ovarian 25 cancer, open paren, EOC, close paren." The</p>

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<p style="text-align: right;">Page 178</p> <p>1 experimental design, that this was "a 2 multi-center study. Preoperative serum CRP 3 was evaluated in 623 patients with EOC. 4 Results were correlated with clinical data." 5 And if you go jump down to the 6 conclusion they write, "Serum CRP can be seen 7 as a novel, widely available, independent 8 prognostic available of ovarian cancer." 9 Did I read that carefully? 10 A. Close enough. 11 Q. Okay. Thank you. 12 So now if you'd look at -- on 13 the first page, in the right column, the very 14 first paragraph, they -- starts off with "the 15 pathogenesis and development of ovarian 16 cancer." 17 Have you seen that? 18 A. Yes. 19 Q. And they write, "The 20 pathogenesis of ovarian cancer -- and 21 development of ovarian cancer have also been 22 closely linked to inflammatory processes, 23 open paren, 6, 7, close paren." 24 Did I read that carefully? 25 MS. MILLER: Did you read it</p>	<p style="text-align: right;">Page 180</p> <p>1 in the history of cancer as centuries go. 2 (Boyd Exhibit 11 marked for 3 identification.) 4 QUESTIONS BY MR. RESTAINO: 5 Q. The reference 7 I've now marked 6 as Boyd 11. It's "Inflammation and Cancer: 7 Back to Virchow." And if you -- if you look 8 down at the lower left, it states that -- all 9 the way down at the bottom -- this was 10 published in the Lancet in 2001; is that 11 correct? 12 A. That is correct. 13 Q. And do you recognize the Lancet 14 as a premier medical journal in the world? 15 MS. MILLER: Objection. 16 THE WITNESS: I recognize the 17 Lancet as a British Medical Journal. 18 QUESTIONS BY MR. RESTAINO: 19 Q. Okay. Do you know what its 20 impact factor is? 21 A. No. 22 Q. Do you know what an impact 23 factor is? 24 A. Yes. 25 Q. Okay. If I represent to you</p>
<p style="text-align: right;">Page 179</p> <p>1 carefully? 2 MR. RESTAINO: Correctly. I'm 3 going to say that all afternoon. 4 THE WITNESS: Yes. 5 QUESTIONS BY MR. RESTAINO: 6 Q. Thank you. 7 And in fact, references 6 and 8 7, if you go to the back, 6 is by the author 9 H-e-l-z-l-s-o-u-e-r, et al., and 7 is 10 Balkwill, Mantovani, "Inflammation and 11 Cancer: Back to Virchow." 12 Did I read that correctly? Or 13 carefully? 14 A. Both. 15 Q. Are you familiar with 16 Dr. Rudolf Virchow, or Virchow? 17 A. I've never met the man. He's 18 been dead for a long time. 19 Q. Yes. 20 But are you familiar with his 21 work? 22 A. I'm relatively -- cottonmouth 23 thing again. Excuse me. 24 I'm relatively familiar with 25 the fact that he was a rather iconic figure</p>	<p style="text-align: right;">Page 181</p> <p>1 that the Lancet has an impact factor of 2 53.24, would that indicate that it has high 3 esteem as a medical journal? 4 A. It would indicate that papers 5 published in that journal are frequently 6 referenced by others. 7 Q. Okay. And the lead author is 8 Fran Balkwill. 9 Do you know her? 10 A. We've met. 11 Q. Have you ever published with 12 her? 13 A. I'm guessing the answer is yes. 14 Q. If -- guessing or estimating? 15 I'll withdraw it. 16 If you turn to the second 17 page -- 18 A. Of? 19 Q. -- of the Balkwill and 20 Mantovani paper. 21 A. Oh, the Lancet. 22 Q. The Lancet paper, okay. 23 And you see they have a -- I'm 24 sorry, it's actually page 541 -- no, excuse 25 me. Give me one moment. I appear to have</p>

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<p style="text-align: right;">Page 182</p> <p>1 marked my...</p> <p>2 Very sorry. Right there in</p> <p>3 front of me.</p> <p>4 The first page, in the lower</p> <p>5 right-hand corner, there's a panel 1:</p> <p>6 Sub-associations between inflammation and</p> <p>7 cancer risk.</p> <p>8 Do you see that, sir?</p> <p>9 A. I do.</p> <p>10 Q. And on the left they list</p> <p>11 malignancy and on the right inflammatory</p> <p>12 stimulus\condition.</p> <p>13 Do you see that, sir?</p> <p>14 A. Yes.</p> <p>15 Q. And if you see the third line</p> <p>16 down under malignancy is listed ovarian. And</p> <p>17 to the right they have pelvic inflammatory</p> <p>18 disease\talc\tissue remodeling.</p> <p>19 Did I read that correctly?</p> <p>20 A. You did.</p> <p>21 Q. So as these authors published</p> <p>22 in Lancet in 2001, talc was listed as one of</p> <p>23 the inflammatory stimuli or conditions which</p> <p>24 could cause ovarian cancer; is that correct?</p> <p>25 MS. MILLER: Objection.</p>	<p style="text-align: right;">Page 184</p> <p>1 they're simply restating the large</p> <p>2 epidemiologic literature that pertains to</p> <p>3 that putative risk.</p> <p>4 Q. Actually, in this area they</p> <p>5 were talking about, Doctor, focusing on the</p> <p>6 role of inflammation, especially chronic</p> <p>7 inflammation, and the development of cancer,</p> <p>8 it is -- we discussed where you wrote that</p> <p>9 "Dr. Saed appears to take for granted that</p> <p>10 ovarian cancer is caused by inflammation,</p> <p>11 but, this, too, has not been established.</p> <p>12 Dr. Saed essentially ignores the body of</p> <p>13 science suggesting that chronic inflammation</p> <p>14 does not play a role in the development of</p> <p>15 ovarian cancer."</p> <p>16 So with that in mind, if you</p> <p>17 look to the left of -- in the left column of</p> <p>18 the Balkwill Lancet paper, the second</p> <p>19 paragraph, you see it starts off "panel 1"?</p> <p>20 So it's left column, front</p> <p>21 page of the Lancet article.</p> <p>22 A. Do you mean right column?</p> <p>23 Q. Left column, second</p> <p>24 paragraph --</p> <p>25 A. Oh, the text that says "panel</p>
<p style="text-align: right;">Page 183</p> <p>1 THE WITNESS: No, that's not</p> <p>2 correct.</p> <p>3 QUESTIONS BY MR. RESTAINO:</p> <p>4 Q. What's incorrect about that?</p> <p>5 A. Panel 1 seems to be a summary</p> <p>6 of their impression of the literature</p> <p>7 suggesting that talc is one of several</p> <p>8 associations that have been noticed -- that</p> <p>9 have been noted with, in this particular</p> <p>10 case, ovarian cancer risk. It has nothing to</p> <p>11 do with -- I mean, this is, after all, a</p> <p>12 review article, and so everything in here is</p> <p>13 a summary of other -- I mean, it's not a</p> <p>14 primary paper.</p> <p>15 Q. In your --</p> <p>16 A. So in other words, Dr. Balkwill</p> <p>17 and her colleague are not providing evidence</p> <p>18 that -- primary evidence that talc is</p> <p>19 associated with ovarian cancer risk. They're</p> <p>20 simply pointing out something that I believe</p> <p>21 we've already agreed to: that there is</p> <p>22 indeed, at least to the extent that I</p> <p>23 understand it, a weak association,</p> <p>24 epidemiologic association, between perineal</p> <p>25 talc use and ovarian cancer risk. And</p>	<p style="text-align: right;">Page 185</p> <p>1 1." Yes.</p> <p>2 Q. Yes.</p> <p>3 "Panel 1 lists some cancers</p> <p>4 where the inflammatory process is a cofactor</p> <p>5 in carcinogenesis."</p> <p>6 Did I read that correctly?</p> <p>7 A. You did.</p> <p>8 Q. And this goes back to, again,</p> <p>9 2001, agreed?</p> <p>10 A. The paper was published in</p> <p>11 2001, yes.</p> <p>12 Q. Now, if you look at the</p> <p>13 abstract, seven lines down, sort of to the</p> <p>14 left, second word, there's a -- the -- first</p> <p>15 there's a word "cancer," and then "if genetic</p> <p>16 damage."</p> <p>17 Do you see that, sir?</p> <p>18 A. Yes.</p> <p>19 Q. "If genetic damage is the,</p> <p>20 quote, match that lights the fire, end quote,</p> <p>21 of cancer, some types of inflammation may</p> <p>22 provide the, quote, fuel that feeds the</p> <p>23 flames, end quote."</p> <p>24 Did I read that correctly?</p> <p>25 A. You did.</p>

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<p style="text-align: right;">Page 186</p> <p>1 Q. And this was published in a 2 peer-reviewed publication in 2001, correct? 3 A. It's a review article that was 4 published in a peer-reviewed publication in 5 2001, that is correct. 6 Q. And a review article is meant 7 to put together the literature for readers so 8 that if one wants to look up a topic, it 9 could be a good starting point for studying 10 that topic; would you agree? 11 MS. MILLER: Objection. 12 THE WITNESS: I know what my 13 purpose in writing a review article 14 is. I can't opine on Dr. Balkwill's 15 goals in writing a review article. 16 (Boyd Exhibit 12 marked for 17 identification.) 18 QUESTIONS BY MR. RESTAINO: 19 Q. Okay. I've now marked as 20 Boyd 12 an article written by Roberta Ness, 21 Carrie Cottreau, titled "Possible Role of 22 Ovarian Epithelial Inflammation in Ovarian 23 Cancer." This was published in the Journal 24 of the National Cancer Institute in 1999. 25 Do you see the -- do you</p>	<p style="text-align: right;">Page 188</p> <p>1 don't know what month it was 2 published, so I was being generous. 3 THE WITNESS: Well, it's fair 4 to say that it was submitted several 5 months before it was ever published, 6 but regardless, I honestly don't 7 remember the paper. 8 QUESTIONS BY MR. RESTAINO: 9 Q. I understand. I'm just asking 10 if you remember. 11 A. No, I don't. 12 Q. You've met Dr. Ness, though. I 13 think that's what you've just testified to? 14 A. Yes. 15 Q. And do you hold her in high 16 esteem as a research scientist? 17 MS. MILLER: Objection. 18 THE WITNESS: I don't hold 19 individuals in high or low or any 20 esteem in terms of research. I prefer 21 to look at the research itself as 22 opposed to making some kind of 23 judgment about the quality of an 24 individual that produced it. 25</p>
<p style="text-align: right;">Page 187</p> <p>1 recognize the Journal of the National Cancer 2 Institute as a highly respected medical 3 journal? 4 A. I recognize it as a 5 peer-reviewed journal. 6 Q. You have six publications in 7 this journal yourself, do you not? 8 A. I couldn't tell you. Or I'm 9 unable to tell you. 10 Q. Okay. Do you know Dr. Roberta 11 Ness? 12 A. We've met. 13 Q. In fact, you've published with 14 her, correct? 15 A. That's something I'll take your 16 word for. I'm sure you're correct. 17 Q. Does the paper "Ovarian Cancer 18 in High Risk Women: Implications for 19 Prevention, Screening and Early Detection," 20 published in Gynecologic Oncology in 2003 21 ring a bell, appreciating that it was 22 15 years ago? 23 MS. MILLER: 16. It's 2019, 24 John. 25 MR. RESTAINO: Yeah, but we</p>	<p style="text-align: right;">Page 189</p> <p>1 QUESTIONS BY MR. RESTAINO: 2 Q. Okay. The paper by Dr. Ness 3 and Dr. Cottreau is "Possible Role of Ovarian 4 Epithelial Inflammation in Ovarian Cancer," 5 correct? 6 A. Still is. 7 Q. So we have the words "ovarian," 8 "inflammation" and "cancer" in the title. 9 Did you see this article when 10 you did your PubMed review of the biomedical 11 literature? 12 A. I think I may have. 13 Q. And did you review this 14 article? 15 A. I may have read the abstract. 16 Q. Well, let's look at the 17 abstract then. 18 And if you look on the third 19 line, starting on the right, "This paper 20 reviews the epidemiologic literature in the 21 English language on risk factors and 22 protective factors for ovarian cancer and 23 proposes a novel hypothesis that a common 24 mechanism underlying this disease is 25 inflammation. Previous hypothesis about the</p>

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<p style="text-align: right;">Page 190</p> <p>1 causes of ovarian cancer have attributed risk</p> <p>2 to an excess number of lifetime ovulations or</p> <p>3 to elevations in steroid hormones.</p> <p>4 Inflammation may underlie ovulatory events</p> <p>5 because an inflammatory reaction is induced</p> <p>6 during the process of ovulation. Additional</p> <p>7 risk factors for ovarian cancer, including</p> <p>8 asbestos and talc exposure, endometriosis,</p> <p>9 open paren, i.e., ectopic implantation of</p> <p>10 uterine lining tissue, close paren, and</p> <p>11 pelvic inflammatory disease, cannot be</p> <p>12 directly linked to ovulation or to hormones</p> <p>13 but do cause pelvic -- local pelvic</p> <p>14 inflammation."</p> <p>15 Did I read this correctly?</p> <p>16 A. Yes.</p> <p>17 Q. Now, do you have the</p> <p>18 physiological expertise to opine on whether</p> <p>19 inflammatory reaction is induced during the</p> <p>20 process of ovulation?</p> <p>21 A. I don't and -- I'm sorry, could</p> <p>22 you repeat the sentence?</p> <p>23 Q. Do you have the physiological</p> <p>24 expertise to opine on whether an inflammatory</p> <p>25 reaction is induced during the process of</p>	<p style="text-align: right;">Page 192</p> <p>1 I think if there were a</p> <p>2 substantial body of experimental data</p> <p>3 demonstrating that inflammation was due --</p> <p>4 produced during the process of human</p> <p>5 ovulation, I would like to see it.</p> <p>6 Throughout this -- the large</p> <p>7 body of this abstract that you just read, she</p> <p>8 used the word "hypothesis" multiple times.</p> <p>9 And I think these are interesting hypotheses.</p> <p>10 My opinion sitting here today</p> <p>11 is that we, the scientific community, really</p> <p>12 have no idea why the ovulatory process</p> <p>13 repeated to an excess as opposed to a lesser</p> <p>14 degree is associated with an increased risk</p> <p>15 of ovarian cancer.</p> <p>16 Q. When you say "we, the</p> <p>17 scientific community," would it surprise you</p> <p>18 to understand that there are other members of</p> <p>19 the scientific community that disagree with</p> <p>20 you in that regard?</p> <p>21 A. That there are data from</p> <p>22 humans -- and this is a question. That there</p> <p>23 are data from humans, human tissues, showing</p> <p>24 that ovulation produces an inflammatory</p> <p>25 response in the ovary?</p>
<p style="text-align: right;">Page 191</p> <p>1 ovulation?</p> <p>2 MS. MILLER: Objection.</p> <p>3 THE WITNESS: Physiologic</p> <p>4 expertise is kind of a weird term.</p> <p>5 I think what you mean to say</p> <p>6 is, do I have the expertise to opine</p> <p>7 on whether --</p> <p>8 QUESTIONS BY MR. RESTAINO:</p> <p>9 Q. On whether an inflammatory</p> <p>10 reaction is induced during ovulation?</p> <p>11 A. I think what you're asking is,</p> <p>12 do I have the expertise to opine on whether</p> <p>13 an inflammatory process is induced during the</p> <p>14 process of ovulation.</p> <p>15 I think expertise is really the</p> <p>16 wrong term here. I think -- I think if there</p> <p>17 were evidence -- I'll start over.</p> <p>18 I think -- I'll start over.</p> <p>19 I know that incessant ovulation</p> <p>20 and all the risk factors and protective</p> <p>21 factors that are associated with incessant</p> <p>22 ovulation, or lack thereof, are to one degree</p> <p>23 or another risk factors for ovarian cancer.</p> <p>24 I believe that. And I think I'm qualified to</p> <p>25 believe that, as we've discussed all morning.</p>	<p style="text-align: right;">Page 193</p> <p>1 Q. Yes.</p> <p>2 A. I would like to see the data.</p> <p>3 Q. You haven't to date?</p> <p>4 A. No.</p> <p>5 Q. Okay. Do you agree with</p> <p>6 Dr. Roberta Ness and Carrie Cottreau when</p> <p>7 they describe asbestos as an additional risk</p> <p>8 factor for ovarian cancer?</p> <p>9 MS. MILLER: Objection. I</p> <p>10 think he said he wasn't offering</p> <p>11 opinions on asbestos.</p> <p>12 MR. RESTAINO: I'm not asking</p> <p>13 if he's got an opinion on asbestos.</p> <p>14 I'm asking if he agrees with this</p> <p>15 published opinion.</p> <p>16 THE WITNESS: Well, if I'm not</p> <p>17 offering an opinion, I'm not going to</p> <p>18 offer an opinion on someone else's</p> <p>19 opinion.</p> <p>20 QUESTIONS BY MR. RESTAINO:</p> <p>21 Q. Okay.</p> <p>22 A. With all due respect.</p> <p>23 Q. Well, do you agree with</p> <p>24 Dr. Roberta Ness and Carrie Cottreau when</p> <p>25 they describe talc exposure as an additional</p>

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<p style="text-align: right;">Page 194</p> <p>1 risk factor for ovarian cancer?</p> <p>2 MS. MILLER: Can you point him</p> <p>3 to what you're talking about?</p> <p>4 THE WITNESS: It's further down</p> <p>5 in the abstract. I'll find it.</p> <p>6 Perhaps further up. Perhaps</p> <p>7 right in the middle.</p> <p>8 Okay. Now I found the</p> <p>9 sentence. Can you please repeat the</p> <p>10 question?</p> <p>11 QUESTIONS BY MR. RESTAINO:</p> <p>12 Q. Do you agree with Drs. Roberta</p> <p>13 Ness and Carrie Cottreau when they describe</p> <p>14 talc exposure as an additional risk factor</p> <p>15 for ovarian cancer?</p> <p>16 MS. MILLER: Objection.</p> <p>17 THE WITNESS: Yeah, I think</p> <p>18 we've covered this multiple times. I</p> <p>19 will agree that there is a limited</p> <p>20 body of weak -- there's a limited body</p> <p>21 of evidence suggesting a very weak</p> <p>22 risk in terms of association of talc</p> <p>23 with ovarian cancer.</p> <p>24 QUESTIONS BY MR. RESTAINO:</p> <p>25 Q. And how do you define very weak</p>	<p style="text-align: right;">Page 196</p> <p>1 A. The population risk of ovarian</p> <p>2 cancer, the general population risk, is</p> <p>3 approximately 1.3. So in other words, 1 out</p> <p>4 of 87 women over a lifetime will develop</p> <p>5 ovarian cancer.</p> <p>6 And so if the relative risk</p> <p>7 associated with a particular exposure is</p> <p>8 increased by 30 percent, when you multiply</p> <p>9 1.3 times 1.3 and you get the risk associated</p> <p>10 with -- again, if we accept the relative risk</p> <p>11 of 1.3, you get the risk associated with talc</p> <p>12 exposure from the association studies.</p> <p>13 Q. Isn't it true that if one is</p> <p>14 looking for an increased risk in a</p> <p>15 population, the background rate from which we</p> <p>16 start is limited to unity or 1.0?</p> <p>17 MS. MILLER: Objection.</p> <p>18 THE WITNESS: 1.0 equals 1.3,</p> <p>19 but I'll stop there. I'm getting out</p> <p>20 of my realm of expertise.</p> <p>21 QUESTIONS BY MR. RESTAINO:</p> <p>22 Q. Okay. If you look at the final</p> <p>23 two sentences of the abstract in the paper by</p> <p>24 Ness and Cottreau, they write, "Inflammation</p> <p>25 entails cell damage."</p>
<p style="text-align: right;">Page 195</p> <p>1 risk in terms of association?</p> <p>2 A. A risk factor of, for example,</p> <p>3 1.2 or 1.3. A relative risk of 1.2 or 1.3.</p> <p>4 Q. I thought you testified earlier</p> <p>5 that you were not an expert in epidemiology.</p> <p>6 Do you understand what a risk</p> <p>7 ratio of 1.2 to 1.3 can equate to --</p> <p>8 MS. MILLER: Objection.</p> <p>9 QUESTIONS BY MR. RESTAINO:</p> <p>10 Q. -- as far as causation?</p> <p>11 MS. MILLER: Objection.</p> <p>12 THE WITNESS: 1.3 times 1.3.</p> <p>13 QUESTIONS BY MR. RESTAINO:</p> <p>14 Q. Do you know how that equates to</p> <p>15 risk?</p> <p>16 A. Yeah. 1.3 is the general</p> <p>17 population risk, times 1.3, would give you</p> <p>18 your increased risk with a relative risk of</p> <p>19 1.3.</p> <p>20 Q. Where are you getting that</p> <p>21 from?</p> <p>22 A. Is that a rhetorical question?</p> <p>23 Q. No.</p> <p>24 What's the basis for that</p> <p>25 opinion?</p>	<p style="text-align: right;">Page 197</p> <p>1 Do you see that down there,</p> <p>2 sir?</p> <p>3 A. I'm sorry, where are we?</p> <p>4 Q. It's approximately five or six</p> <p>5 lines up from the bottom of the abstract.</p> <p>6 "Inflammation entails cell damage" --</p> <p>7 Do you see that?</p> <p>8 A. I see it.</p> <p>9 Q. -- "oxidative stress, elevation</p> <p>10 of cytokines and prostaglandins, all of which</p> <p>11 may be mutagenic. The possibility that</p> <p>12 inflammation is a pathophysiologic</p> <p>13 contributor to the development of ovarian</p> <p>14 cancer suggests a directed approach to future</p> <p>15 research."</p> <p>16 Did I read that correctly?</p> <p>17 A. You did.</p> <p>18 Q. And this was published in 1999,</p> <p>19 correct?</p> <p>20 A. Yes.</p> <p>21 Q. Are you aware of any research</p> <p>22 or experimentation that Johnson &amp; Johnson has</p> <p>23 done since 1999 to either -- to conclude that</p> <p>24 Ness and Cottreau regarding their opinion on</p> <p>25 inflammation and cancer is inaccurate?</p>



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<p style="text-align: right;">Page 198</p> <p>1 A. I'm not aware of any research, 2 again, that Johnson &amp; Johnson has ever 3 performed on anything. 4 Q. Okay. Continuing along with 5 the theme of chronic cancer -- chronic 6 inflammation and ovarian cancer being 7 simplistic at all, I've now marked as Boyd 13 8 a paper by Trabert, T-r-a-b-e-r-t, et al., 9 titled "Prediagnostic Serum Levels of 10 Inflammation Markers and Risk of Ovarian 11 Cancer in the Prostate, Lung, Colorectal and 12 Ovarian Cancer, open paren, PLCO, close 13 paren, Screening Trial." 14 Did I read that correctly? 15 A. Yes. 16 Q. Okay. And if you see up above, 17 this is published in Gynecologic Oncology 18 2014, correct? 19 A. Yes. 20 Q. So we're moving forward from 21 2009. 22 Now, if you look at the list of 23 authors, you see that these individuals are 24 in various divisions, but they're all with 25 the National --</p>	<p style="text-align: right;">Page 200</p> <p>1 evidence implicates chronic inflammation as a 2 central mechanism in the pathogenesis of 3 ovarian cancer, the most lethal gynecologic 4 cancer among women in the United States. 5 Reference 1." 6 Did I read that correctly? 7 A. You did. 8 Q. And reference 1, I'll represent 9 to you, though by all means check, is the 10 Centers for Disease Control and Prevention 11 ovarian cancer statistics, 2010. 12 Did I read that correctly? 13 A. You did. 14 Q. So at this point right now 15 we're talking about researchers from NCI 16 quoting researchers from the CDC, correct? 17 A. Correct. 18 And I would add that my 19 inference from the use of this reference, 20 ovarian cancer statistics, is a reference to 21 support the beginning of this sentence that 22 the most lethal gynecologic cancer among 23 women is ovarian cancer in the United States. 24 That's the statistic to which they're 25 referring.</p>
<p style="text-align: right;">Page 199</p> <p>1 A. National Cancer Institute, yes. 2 I'm sorry. 3 Q. Okay. Do you know any of these 4 authors? 5 A. I may have met Mark Sherman 6 once, but, no, not really. 7 Q. Any reason to believe these 8 researchers with, one, the division of cancer 9 epidemiology and genetics, two, the HPV 10 immunology laboratory and the division of 11 cancer prevention within the National Cancer 12 Institute, are not respected researchers in 13 their respective fields? 14 A. I've already indicated that I 15 don't -- I look at the science that we're 16 discussing. I don't look at the researchers 17 who produced it and try to make a judgment as 18 to whether they're respected or not 19 respected, good people, bad people, 20 good-looking people, not good-looking people. 21 I prefer to discuss the science. 22 Q. Okay. Let's look at the very 23 first sentence on the next page under 24 Introduction. 25 And they write, "Epidemiologic</p>	<p style="text-align: right;">Page 201</p> <p>1 Reference 1 has nothing to do 2 with chronic inflammation as a central 3 mechanism in the pathogenesis of ovarian 4 cancer, I can assure you. 5 Q. And can you point out the CDC 6 document that states that the 7 epidemiologic -- 8 A. If you could produce the 9 document, I'd be happy to read it for you. 10 Q. You didn't pull that document 11 in preparation for writing your expert 12 report? 13 A. I think I actually pull this 14 document every year -- 15 Q. Okay. 16 A. -- because I think it's 17 important to be aware of cancer statistics 18 generally when you're writing review 19 articles. 20 Q. Do you have any objective 21 evidence which refutes the statement by these 22 NCI investigators that epidemiologic evidence 23 implicates chronic inflammation as a central 24 mechanism in the pathogenesis of ovarian 25 cancer?</p>

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<p>1 MS. MILLER: Objection.</p> <p>2 THE WITNESS: I think it's a</p> <p>3 hypothesis, and they haven't provided</p> <p>4 a citation to support the hypothesis.</p> <p>5 They've provided a citation to</p> <p>6 support the fact that epithelial</p> <p>7 ovarian cancer accounts for more</p> <p>8 deaths than all other gynecologic</p> <p>9 cancers combined, which is a fact.</p> <p>10 QUESTIONS BY MR. RESTAINO:</p> <p>11 Q. Doctor, are you guessing</p> <p>12 that's -- that that reference is limited to</p> <p>13 the most lethal gynecologic cancer --</p> <p>14 MS. MILLER: Objection.</p> <p>15 QUESTIONS BY MR. RESTAINO:</p> <p>16 Q. -- portion of their sentence?</p> <p>17 MS. MILLER: Objection. He</p> <p>18 asked to see it.</p> <p>19 THE WITNESS: Could you please</p> <p>20 repeat the question?</p> <p>21 QUESTIONS BY MR. RESTAINO:</p> <p>22 Q. Are you guessing that the</p> <p>23 reference to the CDC is only for the second</p> <p>24 half of that sentence?</p> <p>25 MS. MILLER: Objection.</p>	<p>1 division?</p> <p>2 A. Well, first of all, my</p> <p>3 understanding of this sentence is they're</p> <p>4 talking about cancer generally, and they're</p> <p>5 making some interesting hypotheses. And</p> <p>6 there are no citations to support any of the</p> <p>7 hypotheses in that sentence.</p> <p>8 Q. So does the lack of citations</p> <p>9 render a sentence unbelievable?</p> <p>10 A. No.</p> <p>11 MS. MILLER: Objection.</p> <p>12 Can you give me a second to</p> <p>13 object?</p> <p>14 THE WITNESS: It's not</p> <p>15 unbelievable. I just think that these</p> <p>16 are hypotheses that they're stating.</p> <p>17 I think they're trying to cover the</p> <p>18 waterfront in terms of all the</p> <p>19 hypotheses that have ever been</p> <p>20 rendered with respect to pathogenesis</p> <p>21 of ovarian cancer.</p> <p>22 QUESTIONS BY MR. RESTAINO:</p> <p>23 Q. And when you say "I think</p> <p>24 they're trying to cover the waterfront," are</p> <p>25 you speculating as to their intent in writing</p>
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<p>1 THE WITNESS: I'd like to see</p> <p>2 it, and we can confirm whether it is</p> <p>3 or not.</p> <p>4 QUESTIONS BY MR. RESTAINO:</p> <p>5 Q. Well, this paper with</p> <p>6 inflammation, ovarian and cancer twice in the</p> <p>7 title, did this paper come up during your</p> <p>8 review of the biomedical literature?</p> <p>9 A. Yes.</p> <p>10 Q. Did you review this article at</p> <p>11 that time?</p> <p>12 A. I read the abstract.</p> <p>13 Q. And -- okay. We'll leave it to</p> <p>14 that.</p> <p>15 The next sentence they write</p> <p>16 is, "Chronic inflammation can induce rapid</p> <p>17 cell division, increasing the possibility for</p> <p>18 replication error in effective DNA repair and</p> <p>19 subsequent mutation."</p> <p>20 Did I read that correctly?</p> <p>21 A. You did.</p> <p>22 Q. And do you have any objective</p> <p>23 evidence with which to contradict these NCI</p> <p>24 researchers when they stated in 2014 that</p> <p>25 chronic inflammation can induce rapid cell</p>	<p>1 this article?</p> <p>2 MS. MILLER: Objection.</p> <p>3 THE WITNESS: Yes.</p> <p>4 QUESTIONS BY MR. RESTAINO:</p> <p>5 Q. Okay. And, Doctor, do you have</p> <p>6 any objective evidence with which to</p> <p>7 contradict these NCI researchers when they</p> <p>8 state that "rapid cell division increases the</p> <p>9 possibility for replication error,</p> <p>10 ineffective DNA repair and subsequent</p> <p>11 mutation"?</p> <p>12 MS. MILLER: Objection.</p> <p>13 THE WITNESS: Again, that's</p> <p>14 producing negative data.</p> <p>15 No, it's impossible. I'm</p> <p>16 shaking my head, too.</p> <p>17 QUESTIONS BY MR. RESTAINO:</p> <p>18 Q. Yeah, there's a couple of times</p> <p>19 you said "generating negative data."</p> <p>20 If you do an experiment to test</p> <p>21 the effects of a drug on the treatment for</p> <p>22 ovarian cancer and the drug is an abject</p> <p>23 failure, that's negative data, isn't it?</p> <p>24 MS. MILLER: Objection.</p> <p>25 THE WITNESS: We're talking</p>

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<p style="text-align: right;">Page 206</p> <p>1 about two different things here.  2 QUESTIONS BY MR. RESTAINO:  3 Q. I'm not sure that we are. I'm  4 not sure you understand what negative means.  5 A. A negative result -- excuse me?  6 Please say that again?  7 Q. I'm not sure we are. I'm not  8 sure you understand what negative means in  9 this context.  10 A. I am pretty sure I do.  11 Q. Well, we're finding out, and so  12 far --  13 A. You disagree with me.  14 Q. -- not looking good.  15 I'm sorry?  16 A. Who's not looking good?  17 Q. Okay. Let's go back to 1.3  18 times 1.3.  19 Doctor, is limited  20 replication --  21 A. Let's go back to 1.3 times 1.3.  22 Q. Is limitless replicative  23 potential one of the hallmarks of cancer?  24 A. According to who?  25 Q. According to cancer</p>	<p style="text-align: right;">Page 208</p> <p>1 metastasis?  2 A. If you're going to go down the  3 list of the Hanahan Weinberg paper, it's  4 going to be the same answer.  5 Q. Sustained angiogenesis?  6 A. I've answered your question.  7 Q. I want to get it on the record,  8 sir.  9 Is that a hallmark of cancer?  10 MS. MILLER: Objection. It is  11 on the record because he answered your  12 question already.  13 THE WITNESS: You seem to be  14 reading from the list of hallmarks of  15 cancer as articulated by Hanahan and  16 Weinberg in 2011. And to the extent  17 that your intention it to continue  18 reading down the list, my answer is, I  19 believe that Hanahan and Weinberg  20 believe that these are hallmarks of  21 the cancer phenotype.  22 QUESTIONS BY MR. RESTAINO:  23 Q. Hanahan and Weinberg believe.  24 Do you know if it's generally  25 accepted in the scientific community that</p>
<p style="text-align: right;">Page 207</p> <p>1 specialists.  2 A. Show me what cancer specialists  3 you're talking about and where it's stated.  4 Q. Okay. Is self-sufficiency in  5 growth signaling a hallmark of cancer?  6 A. Are we getting back to Hanahan  7 and Weinberg?  8 Q. I'm just asking you about  9 hallmarks of cancer right now.  10 MS. MILLER: I guess it's been  11 asked and answered in that case.  12 THE WITNESS: I would agree  13 that Hanahan and Weinberg have written  14 a review article suggesting that the  15 last two phenotypic properties of  16 cancer cells are hallmarks of cancer  17 in their opinions.  18 QUESTIONS BY MR. RESTAINO:  19 Q. Is self-sufficiency in growth  20 signaling --  21 A. Same answer.  22 Q. -- the hallmarks --  23 A. If you're going to go down the  24 list, it's going to be the same answer.  25 Q. -- tissue invasion and</p>	<p style="text-align: right;">Page 209</p> <p>1 these are the hallmarks of cancer?  2 MS. MILLER: Objection.  3 THE WITNESS: I can't answer as  4 to what the scientific community  5 believes with respect to the Hanahan  6 and Weinberg paper.  7 QUESTIONS BY MR. RESTAINO:  8 Q. If we look at the Trabert  9 paper, in the next sentence, which is the  10 fourth line under Introduction, all the way  11 to the far right it starts with the word  12 "ovarian."  13 Do you see where I am, sir?  14 A. "Ovarian cancer has been  15 linked"?  16 Q. Yes.  17 A. Yes.  18 Q. "Ovarian cancer has been linked  19 to several events and conditions which are  20 related to inflammation and repair, including  21 incessant ovulation, endometriosis, exposure  22 to talc and asbestos, and in some studies,  23 pelvic inflammatory disease."  24 Did I read that correctly?  25 A. Yes.</p>

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<p style="text-align: right;">Page 210</p> <p>1 Q. And, Doctor, do you have any 2 objective evidence with which to contradict 3 these NCI researchers when they state that 4 "ovarian cancer has been linked to several 5 events and conditions which are related to 6 inflammation and repair"?</p> <p>7 MS. MILLER: I'm a little bit 8 lost. Where are you? What page?</p> <p>9 MR. RESTAINO: I'm on page 2 of 10 the Trabert paper under Introduction. 11 It's the fourth line of the first 12 paragraph.</p> <p>13 MS. MILLER: You read really 14 fast.</p> <p>15 THE WITNESS: I would suggest 16 that these are hypotheses. The 17 reference being cited is another 18 review article by these same authors 19 entitled "Possible Role of Ovarian 20 Epithelial Inflammation and Ovarian 21 Cancer."</p> <p>22 I do not consider a 23 self-reference of another review 24 article, the first word of which is 25 "possible," to be evidence that this</p>	<p style="text-align: right;">Page 212</p> <p>1 inflammatory disease."</p> <p>2 Do you disagree that the 3 ovarian cancer has been linked to several 4 events and conditions which are related to 5 inflammation?</p> <p>6 MS. MILLER: Objection.</p> <p>7 THE WITNESS: It depends.</p> <p>8 QUESTIONS BY MR. RESTAINO:</p> <p>9 Q. Upon?</p> <p>10 A. What type of inflammation and 11 in what context. What type of ovarian 12 cancer.</p> <p>13 Q. Okay. Is there a difference in 14 your mind between the type of ovarian cancer 15 and whether it's associated with chronic 16 inflammation or not?</p> <p>17 A. I agree I -- let me correct 18 myself. My opinion generally is that it's 19 extraordinarily important to define which 20 type of the many types of ovarian cancer 21 we're discussing when we're hypothesizing 22 that one or another type of ovarian cancer 23 may be linked to one or another exposure or 24 physiologic condition. 25 Are you with me?</p>
<p style="text-align: right;">Page 211</p> <p>1 is, in fact, the case.</p> <p>2 QUESTIONS BY MR. RESTAINO:</p> <p>3 Q. Okay. Do you disagree with the 4 statement that "ovarian cancer has been 5 linked to several events and conditions which 6 are related to inflammation and repair"?</p> <p>7 MS. MILLER: Objection.</p> <p>8 THE WITNESS: Well, you're 9 going to have to parse the 10 inflammation and repair. I'm assuming 11 you read it, and it's a poorly 12 constructed sentence.</p> <p>13 What kind of repair, for 14 example?</p> <p>15 QUESTIONS BY MR. RESTAINO:</p> <p>16 Q. The sentence above that we were 17 discussing, they are talking about 18 ineffective DNA repair, correct?</p> <p>19 A. They were.</p> <p>20 Q. Okay. So now they state, 21 "Ovarian cancer has been linked to several 22 events and conditions which are related to 23 inflammation and repair, including incessant 24 ovulation, endometriosis, exposure to talc 25 and asbestos, and in some cases pelvic</p>	<p style="text-align: right;">Page 213</p> <p>1 Q. I'm with you.</p> <p>2 Can you list for us today as 3 you sit here the different types of ovarian 4 cancer?</p> <p>5 A. Broadly speaking.</p> <p>6 Q. Specifically speaking?</p> <p>7 A. Well, that's an impossible 8 question to answer.</p> <p>9 Are you talking about 10 histologic subtypes, or are you talking about 11 epithelial ovarian cancers versus sex cord 12 stromal tumors and germ cell tumors? I mean, 13 what --</p> <p>14 Q. Well, the first -- the last 15 ones you described are different forms of 16 histologic subtypes, correct?</p> <p>17 So to make it easy for you, 18 whichever one you're --</p> <p>19 A. You don't need to make it easy 20 for me. I'm pretty familiar with the 21 subtypes of ovarian cancer.</p> <p>22 Q. Okay. Which form of ovarian 23 cancer has not been linked to chronic 24 inflammation? 25 MS. MILLER: Objection.</p>

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<p style="text-align: right;">Page 214</p> <p>1 THE WITNESS: That's frankly a 2 ridiculous question. 3 (Boyd Exhibit 13 marked for 4 identification.) 5 QUESTIONS BY MR. RESTAINO: 6 Q. Is that so? Can I assume that 7 you can't answer that? 8 MS. MILLER: Objection. 9 THE WITNESS: I did answer. 10 QUESTIONS BY MR. RESTAINO: 11 Q. Do you know the answer to it? 12 MS. MILLER: Does this relate 13 to the pending question? 14 MR. RESTAINO: No, it's coming 15 next. 16 MS. MILLER: Okay. 17 THE WITNESS: I'm saying it's 18 impossible to answer a ridiculous 19 question, in my mind. 20 QUESTIONS BY MR. RESTAINO: 21 Q. Okay. Doctor, I've just marked 22 as Exhibit 14 and handed to you the 2000 23 paper by Hanahan and Weinberg that we've been 24 discussing, correct? 25 MS. MILLER: I'm confused. You</p>	<p style="text-align: right;">Page 216</p> <p>1 as they describe underneath there, the 2 acquired capabilities of cancer we've been 3 discussing; is that correct? 4 A. This is the list that you were 5 reciting, to the best of my knowledge. 6 And I should note further that 7 the caption to the figure reads, "We suggest 8 that most, if not all, cancers" -- and I 9 would insert the word "generally" there -- 10 "have acquired the same set of functional 11 capabilities during their development, albeit 12 through various mechanistic strategy." 13 So in other words, I believe 14 that they're talking about a suggestion in 15 this case that cancers generally have these 16 phenotypic properties, or display these 17 phenotypic properties. 18 Q. And now I suggest -- as you 19 suggested perhaps when you read Dr. Shih's 20 deposition transcript, I represented to him 21 how often this paper has been cited. And now 22 I'll represent to you, in the week or so 23 that's passed, this paper has been cited 24 30,148 times. 25 MS. MILLER: In one week?</p>
<p style="text-align: right;">Page 215</p> <p>1 didn't mark this earlier? You just 2 discussed it? 3 MR. RESTAINO: Yeah. 4 THE WITNESS: Well, this is the 5 first iteration of a paper by the same 6 title published in 2011, but you've 7 handed me a paper by Hanahan and 8 Weinberg published in 2000 called "The 9 Hallmarks of Cancer," yes. 10 QUESTIONS BY MR. RESTAINO: 11 Q. Okay. And if you turn to 12 page 2, there's a diagram with the hallmarks, 13 the acquired capabilities of cancer, as 14 listed by these authors on the bottom of it. 15 And that's what we've been 16 describing, correct? 17 A. I'm sorry, we're looking at 18 Figure 1 -- 19 Q. Yes, sir. 20 A. -- on page 2? 21 Q. Yes, sir. 22 A. And what's the question about 23 Figure 1? 24 Q. Oh, that's the diagram 25 representative of the hallmarks of cancer or,</p>	<p style="text-align: right;">Page 217</p> <p>1 MR. RESTAINO: In total. 2 MS. MILLER: Oh, you're saying 3 you're updating the number. 4 MR. RESTAINO: I'm updating the 5 number. 6 MS. MILLER: I thought you were 7 saying in one week. 8 QUESTIONS BY MR. RESTAINO: 9 Q. As you sit here today, are you 10 aware of any single medical paper that has 11 been referenced more than 30,148 times? 12 A. Well, not without spending more 13 time than we're going to allow to think about 14 it, no. 15 Q. I'll help you. 16 (Boyd Exhibit 14 marked for 17 identification.) 18 QUESTIONS BY MR. RESTAINO: 19 Q. I've now marked as Boyd 20 Exhibit 15 the 2000 publication by Hanahan -- 21 MS. MILLER: That was the 2000 22 publication. Do you mean -- 23 QUESTIONS BY MR. RESTAINO: 24 Q. -- the 2011 publication by 25 Hanahan and Weinberg titled "Hallmarks of</p>

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<p style="text-align: right;">Page 218</p> <p>1 Cancer: The Next Generation." And I'll 2 represent to you that this one has been cited 3 34,389 times as of last night. 4 Doctor, as a cancer researcher, 5 would you agree this is a very important 6 paper in the field of cancer? 7 A. I believe that it's been cited 8 a lot. 9 Q. Okay. Now, on page 2, they 10 have the illustration of the hallmarks of 11 cancer that they first published in 2000, 12 correct? 13 A. It's very similar, yes. 14 Q. Okay. And then on page 658 of 15 the paper, they have an updated diagram 16 there. 17 Do you see that, sir? 18 A. Yes. 19 Q. And on the top they have listed 20 emerging hallmarks, and below that enabling 21 characteristics. 22 Is that correct? 23 A. Yes. 24 Q. And see in the figure right, 25 the legend, the wording to the right of it,</p>	<p style="text-align: right;">Page 220</p> <p>1 all cancers generally and no cancer 2 specifically. 3 QUESTIONS BY MR. RESTAINO: 4 Q. Where are you getting the word 5 "hypothesis" from this when they state that 6 the hallmark is now "widely appreciated as 7 tumor-promoting consequences of an 8 inflammatory response"? 9 A. Because it strikes me as a 10 hypothetical statement without -- without 11 listing all of the known human cancers and 12 evidence that inflammation, et cetera, et 13 cetera, et cetera, is now widely appreciated 14 and so forth. 15 Widely appreciated by whom? 16 Q. As a cancer researcher, do you 17 have to understand the individual mechanisms 18 behind the development of each and every 19 different form of lung cancer that develops 20 in long-term smokers, i.e., non-small cell, 21 small cell, old cell? 22 In order to come to the 23 conclusion that smoking cigarettes causes 24 lung cancer, do you have to see the mechanism 25 for each and every individual one of those</p>
<p style="text-align: right;">Page 219</p> <p>1 if you go all the way down to the bottom, 2 there's one, two, three, four, five, six -- 3 seven lines up from the bottom starts off at 4 right with "inflammation." 5 Do you see that word, sir? 6 A. Yes. 7 Q. "Inflammation by innate immune 8 cells designed to fight infections and heal 9 wounds can instead result in their 10 inadvertent support of multiple hallmark 11 capabilities, thereby manifesting the now 12 widely appreciated tumor-promoting 13 consequences of inflammatory responses." 14 Did I read that correctly? 15 A. You did. 16 Q. And do you have any objective 17 evidence with which to contradict Hanahan and 18 Weinberg in this 2011 peer-reviewed, 19 published paper that the tumor-promoting 20 consequences of inflammatory responses is now 21 widely appreciated? 22 MS. MILLER: Objection. 23 THE WITNESS: Well, first, I 24 would suggest that this is a 25 hypothesis that is used to refer to</p>	<p style="text-align: right;">Page 221</p> <p>1 cancers? 2 MS. MILLER: Objection. 3 THE WITNESS: My impression is 4 that we're litigating ovarian cancer. 5 QUESTIONS BY MR. RESTAINO: 6 Q. But you've brought up several 7 times that authors appear to be relating 8 their information to cancer in general. So 9 my question goes back to that. Being 10 specific, we're talking about lung cancer and 11 smoking. 12 Does smoking cause lung cancer? 13 MS. MILLER: Objection. 14 THE WITNESS: Smoking can cause 15 lung cancer. And I would further add 16 that the epidemiologic association of 17 cigarette smoking with lung cancer is 18 so strong that it's possible to accept 19 that the association is real in terms 20 of causation. 21 QUESTIONS BY MR. RESTAINO: 22 Q. What is the epidemiologic 23 association of passive smoke inhalation and 24 lung cancer? 25 A. Do not know.</p>



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<p style="text-align: right;">Page 222</p> <p>1 Q. Would it surprise you to know 2 that it's 1.3? 3 A. No. 4 Q. If you turn to page 659 of 5 Hanahan and Weinberg, there's a first -- 6 there's a full paragraph on the right column 7 that starts "by 2000." 8 Do you see that, sir? 9 A. Yes. 10 Q. "By 2000, there are already 11 clues that the tumor-associated inflammatory 12 response had the unanticipated, paradoxical 13 effect of enhancing tumorigenesis and 14 progression, in effect helping incipient 15 neoplasias to acquire hallmark capabilities." 16 Did I read that correctly? 17 A. You did. 18 Q. Doctor, what is meant by 19 tumorigenesis? 20 A. The genesis of tumors. 21 Q. And how would you define tumor 22 regression? 23 A. It's a term that we don't 24 really use anymore. Initiation, promotion 25 and regression. They were useful decades</p>	<p style="text-align: right;">Page 224</p> <p>1 Q. You want to look at the 2 references? 3 A. Could we? 4 Q. Of course. 5 A. Yes. 6 Q. Okay. 7 A. These papers are referring to 8 existing cancers and either progression 9 and/or metastasis of existing cancers, not 10 the initiation of cancer, that is, the events 11 involved in -- the very early events involved 12 in the transformation process leading a 13 normal cell to become malignant and 14 ultimately metastatic. 15 So -- 16 Q. And in fact, Doctor, right 17 above the references they write, the last 18 four words, "have on neoplastic progression." 19 And that was the context of my question. 20 A. I think they're talking about 21 existing cancers. 22 Q. Yes. And progression of 23 existing cancer. 24 My only question was going to 25 be here, neoplastic progression, would you</p>
<p style="text-align: right;">Page 223</p> <p>1 ago, but we now like to refer to it a 2 multi-genetic, multi-step process. 3 Q. Has progression been absorbed 4 into that multi-genetic, multi-step process? 5 A. I think that's a fair 6 statement. 7 Q. Okay. The next sentence they 8 write here is, "In the ensuing decade, 9 research on the intersections between 10 inflammation and cancer pathogenesis has 11 blossomed producing abundant and compelling 12 demonstrations of the functionally important 13 tumor-promoting effects that immune cells, 14 hyphen, largely of the innate immune system, 15 hyphen, have on neoplastic progression." 16 Did I read that correctly? 17 A. You did. 18 Q. And there are four citations 19 there, correct? 20 A. Correct. 21 Q. And once again, here when they 22 write "neoplastic progression," would that be 23 something that you -- 24 A. Can we look at -- I'm sorry, go 25 ahead.</p>	<p style="text-align: right;">Page 225</p> <p>1 then encompass this term in the more modern 2 one that you were just sharing with us? 3 A. I would say that the entire 4 concept is irrelevant to the arguments that 5 we're having here today about whether talc 6 initiates ovarian tumorigenesis or not. 7 Q. Okay. Is it relevant to the 8 argument as to whether or not the plaintiff 9 experts' reliance upon chronic inflammation 10 is simplistic? 11 A. Couldn't follow your sentence. 12 Sorry. 13 Q. Okay. You stated earlier that 14 the opinions regarding chronic inflammation, 15 whether it was the plaintiff experts or 16 Dr. Saed, were -- and I can't paraphrase it 17 all, but the one word you used was 18 "simplistic," correct? You remember that? 19 A. Vaguely. 20 Q. And we've now gone through Ness 21 and Cottreau in 2009; Trabert, et al., in 22 2014; CDC in 2014. Now we're looking at 23 Hanahan 2011 talking about inflammation, and 24 not only initiation but also progression of 25 cancer. That's the only context I'm using</p>



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<p>1 this for.</p> <p>2 MS. MILLER: Is that a</p> <p>3 question?</p> <p>4 MR. RESTAINO: No, it was an</p> <p>5 explanation to why we were in this</p> <p>6 area.</p> <p>7 THE WITNESS: It sounded like a</p> <p>8 speech, but that's all right.</p> <p>9 QUESTIONS BY MR. RESTAINO:</p> <p>10 Q. It was just an explanation of</p> <p>11 why we're in this area.</p> <p>12 Let's go to the</p> <p>13 self-sufficiency in growth signals.</p> <p>14 As described by Hanahan --</p> <p>15 MS. MILLER: You got to slow</p> <p>16 down. Where are you?</p> <p>17 MR. RESTAINO: It's just one of</p> <p>18 the hallmarks. I'm just describing</p> <p>19 the term.</p> <p>20 MS. MILLER: What page? Where</p> <p>21 are you reading from?</p> <p>22 MR. RESTAINO: Well, any one of</p> <p>23 either the 2000 paper or the 2000 --</p> <p>24 THE WITNESS: But where in the</p> <p>25 paper, I think --</p>	<p>1 research paper, I will disagree with</p> <p>2 the doctor when you refer -- as to its</p> <p>3 implications in the medical</p> <p>4 literature.</p> <p>5 Secondly, I'm just asking in a</p> <p>6 general sense as to a cancer</p> <p>7 specialist --</p> <p>8 MS. MILLER: Okay. You just --</p> <p>9 you have the exhibit open. I'm</p> <p>10 confused. I didn't know if you were</p> <p>11 reading or asking a question.</p> <p>12 QUESTIONS BY MR. RESTAINO:</p> <p>13 Q. Doctor, generically speaking,</p> <p>14 is self-sufficiency in growth signals one of</p> <p>15 the hallmarks of any cancer?</p> <p>16 MS. MILLER: Objection.</p> <p>17 THE WITNESS: Where does it say</p> <p>18 self-sufficiency in growth signaling?</p> <p>19 MS. MILLER: I think he's</p> <p>20 saying that he's just asking this</p> <p>21 question unrelated to this document.</p> <p>22 I think. I'm confused as well.</p> <p>23 THE WITNESS: You'll have to</p> <p>24 explain your definition of</p> <p>25 self-sufficiency to me, please.</p>
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<p>1 MS. MILLER: We're on the 2011</p> <p>2 paper. That's my understanding.</p> <p>3 QUESTIONS BY MR. RESTAINO:</p> <p>4 Q. So go to the second column --</p> <p>5 or the second page.</p> <p>6 MS. MILLER: I think you don't</p> <p>7 realize you read very fast and you</p> <p>8 don't give page numbers, and I get</p> <p>9 very confused.</p> <p>10 MR. RESTAINO: But I wasn't</p> <p>11 reading from anything.</p> <p>12 MS. MILLER: You were reading</p> <p>13 from something. Nobody can talk that</p> <p>14 fast without reading.</p> <p>15 QUESTIONS BY MR. RESTAINO:</p> <p>16 Q. Doctor, sustaining</p> <p>17 proliferative signaling, can that lead to</p> <p>18 self-sufficiency in growth signals?</p> <p>19 MS. MILLER: I'm sorry, is this</p> <p>20 question based on this study or</p> <p>21 this -- sorry, it's not a study. It's</p> <p>22 a review article, I think you said?</p> <p>23 Is this question related to</p> <p>24 this exhibit?</p> <p>25 MR. RESTAINO: First of all, a</p>	<p>1 QUESTIONS BY MR. RESTAINO:</p> <p>2 Q. Could you pick up what is</p> <p>3 previously marked as Exhibit 14?</p> <p>4 A. Okay. We're back to 14. I'm</p> <p>5 sorry.</p> <p>6 Q. The 2000 paper, hallmarks of</p> <p>7 cancer.</p> <p>8 A. We're going back to 2000?</p> <p>9 Q. Yes.</p> <p>10 A. Okay.</p> <p>11 Q. Open to the second page.</p> <p>12 See the diagram, Figure 1?</p> <p>13 A. Yes.</p> <p>14 Q. You see the first acquired</p> <p>15 capability of cancer up at the top of it?</p> <p>16 A. Yes.</p> <p>17 Q. Is it titled "Self-Sufficiency</p> <p>18 in Growth Signals"?</p> <p>19 A. Yes, it was in 2000.</p> <p>20 And then in 2011 they changed</p> <p>21 the same phenotype to sustaining</p> <p>22 proliferative signaling.</p> <p>23 I would agree generally that</p> <p>24 sustained proliferative signaling is a</p> <p>25 hallmark of cancer, generally speaking.</p>

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<p style="text-align: right;">Page 230</p> <p>1 Q. Is it also a hallmark of 2 ovarian cancer? 3 A. Yes, generally speaking. 4 Q. Looking at the 2000 paper 5 again, the hallmark down below that, to the 6 right is "insensitivity to anti-growth 7 signals." 8 Is that a hallmark of cancer, 9 generally? 10 MS. MILLER: Objection. 11 THE WITNESS: Well, I would 12 simply agree with the authors that 13 suggest, "We suggest that most, if not 14 all, cancers have acquired the same 15 set of functional capabilities during 16 their development, albeit through very 17 mechanistic strategies." 18 I would agree with the 19 statement underneath the figure. 20 QUESTIONS BY MR. RESTAINO: 21 Q. Okay. Would you, as an expert 22 in ovarian cancer research, agree that 23 insensitivity to anti-growth signals occurs 24 in ovarian cancer also? 25 A. Yes. As I have previously</p>	<p style="text-align: right;">Page 232</p> <p>1 A. Yes, it's associated with, 2 again, mutational inactivation of the TP53 3 gene, which is extraordinarily common in 4 serous ovarian epithelial carcinomas and 5 indeed is the most frequently mutated tumor 6 suppressor gene in all cancers generally. 7 Q. Okay. All three of these will 8 lead to cellular proliferation, correct? 9 MS. MILLER: Objection. 10 All three of what? 11 QUESTIONS BY MR. RESTAINO: 12 Q. All three of these hallmarks 13 that we've just discussed. 14 MS. MILLER: Can you identify 15 which three you're referring to? 16 THE WITNESS: It's -- he's 17 referring to the top -- the three at 18 the top of Figure 1 in exhibit -- so 19 if we look at Figure 1 in Exhibit 14, 20 he's referring to the top three 21 phenotypic properties of acquired 22 capabilities of cancer. 23 QUESTIONS BY MR. RESTAINO: 24 Q. And the result of these three 25 hallmarks is going to be cellular</p>
<p style="text-align: right;">Page 231</p> <p>1 indicated, all cancers, including ovarian 2 cancers, are associated with the occurrence 3 and accumulation of mutations and oncogenes 4 and tumor suppressor genes. 5 The normal function of a tumor 6 suppressor gene is to inhibit growth, so in 7 other words, to provide an anti-growth 8 signal. And so when a tumor suppressor gene 9 such as TP53 or RB1 is inactivated, which 10 occurs frequently in ovarian cancer, then the 11 ovarian cancer cells become insensitive to 12 anti-growth signal. 13 Q. Okay. To the left of that 14 hallmark they write "evading apoptosis. " 15 Do you see that, sir? 16 A. Yes. 17 Q. And apoptosis is the death of 18 cells which occurs as a normal, controlled 19 part of an organism's growth and development; 20 would you agree? 21 A. It's generally referred to as 22 programmed cell death, but, yes. 23 Q. Fair enough. 24 Is evading apoptosis one of the 25 hallmarks, generally speaking, of cancer?</p>	<p style="text-align: right;">Page 233</p> <p>1 proliferation; would you agree? 2 A. Not necessarily, but would 3 certainly be more likely under these 4 circumstances than if these mutational events 5 leading to these phenotypic properties had 6 not occurred. 7 Q. Okay. 8 A. Tumor cells are not constantly 9 dividing. 10 Q. Let's turn to your expert 11 report, page 4. And you have a section 12 there, A, study design issues. The first one 13 is the use of DMSO as a solvent. 14 Did I read that correctly? 15 A. Yes. 16 Well, mostly correctly. 17 Q. Do you see the section "use of 18 DMSO as solvent"? 19 A. Yes. 20 Q. Okay. Colon. 21 And then you write in your 22 paragraph there -- if you look five lines 23 down, sir, towards the right, there's a 24 sentence where you start with, "But he 25 apparently paid."</p>

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<p>1 Do you see that?</p> <p>2 A. Yes.</p> <p>3 Q. "But he apparently paid no heed</p> <p>4 to recent research that has called into</p> <p>5 question whether the use of DMSO as a solvent</p> <p>6 can alter the effect of the treatment and</p> <p>7 skew the results."</p> <p>8 Reference 7 down below, Hall,</p> <p>9 MD, et al., "Say No to DMSO:</p> <p>10 Dimethylsulfoxide Inactivates Cisplatin,</p> <p>11 Carboplatin and Other Platinum Complexes."</p> <p>12 Did I read that correctly?</p> <p>13 A. You did.</p> <p>14 (Boyd Exhibit 16 marked for</p> <p>15 identification.)</p> <p>16 QUESTIONS BY MR. RESTAINO:</p> <p>17 Q. So I've marked as Boyd 16 your</p> <p>18 reference by Hall, et al. "Say no to DMSO."</p> <p>19 MS. MILLER: It's very catchy.</p> <p>20 MR. RESTAINO: It is. Easy to</p> <p>21 remember.</p> <p>22 QUESTIONS BY MR. RESTAINO:</p> <p>23 Q. Did I read that correctly, sir?</p> <p>24 Well, strike that.</p> <p>25 You recognize this paper,</p>	<p>1 typical in terms of a ligand receptor</p> <p>2 interaction such as epidermal growth factor,</p> <p>3 epidermal growth factor receptor being a</p> <p>4 ligand receptor interaction.</p> <p>5 So ligand actually has many</p> <p>6 definitions, depending on the context. The</p> <p>7 one you're using now is a chemical context,</p> <p>8 and I do not hold myself out as a chemist.</p> <p>9 Q. Okay. Do you agree that DMSO</p> <p>10 is a virtual, universal solvent?</p> <p>11 A. I believe that</p> <p>12 dimethylsulfoxide is used very commonly to</p> <p>13 dissolve chemicals of all kinds in an</p> <p>14 experimental context because many chemicals</p> <p>15 are readily soluble in DMSO.</p> <p>16 Q. So you're not disagreeing with</p> <p>17 Hall, et al., if they describe it as a</p> <p>18 virtual, universal solvent?</p> <p>19 A. I think that's a fair</p> <p>20 description of DMSO in this particular</p> <p>21 context.</p> <p>22 Q. Okay. Now, where I'm reading</p> <p>23 from, sir, is -- I'm not trying to play any</p> <p>24 word games from you -- is page 2, the middle</p> <p>25 paragraph under Introduction.</p>
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<p>1 correct, sir?</p> <p>2 A. Yes.</p> <p>3 Q. Now, early on I asked you if</p> <p>4 you were an expert in pharmacology, and you</p> <p>5 said you were not, correct?</p> <p>6 A. Correct.</p> <p>7 Q. But do you have a basic</p> <p>8 understanding what the platinum-based drugs</p> <p>9 cisplatin, carboplatin and oxaliplatin are?</p> <p>10 A. Oxaliplatin.</p> <p>11 Q. That one, too.</p> <p>12 A. Yes.</p> <p>13 Q. Do you understand that they</p> <p>14 contain a ligand attached to them?</p> <p>15 A. Are you referring to platinum</p> <p>16 as a ligand?</p> <p>17 Q. Sir, do you know what a ligand</p> <p>18 is?</p> <p>19 A. It's -- I think what you're</p> <p>20 trying to get at is a ligand may generally be</p> <p>21 used as a definition for a molecule that</p> <p>22 interacts with another molecule.</p> <p>23 Earlier when we were discussing</p> <p>24 ligand, I was thinking of ligand in a cell</p> <p>25 biological context, which is much more</p>	<p>1 And all I can say is it's in</p> <p>2 the middle of the paragraph. The universal</p> <p>3 solvent language is there on the right-hand</p> <p>4 side about 11, maybe 12 lines down.</p> <p>5 A. Uh-huh.</p> <p>6 Q. Do you see that, sir?</p> <p>7 A. Yes.</p> <p>8 Q. And then a sentence ends with a</p> <p>9 reference 12, correct?</p> <p>10 A. Yes.</p> <p>11 Q. And then they write, "DMSO</p> <p>12 contains a nucleophilic sulfur, which allows</p> <p>13 it to coordinate with platinum complexes,</p> <p>14 displacing ligands and changing the structure</p> <p>15 of the complexes, open paren, 13 to 16. This</p> <p>16 renders platinum complexes unstable in DMSO."</p> <p>17 Did I read that correctly?</p> <p>18 A. I lost you, but I'll submit</p> <p>19 that you did.</p> <p>20 Q. Want me to read it again?</p> <p>21 A. No.</p> <p>22 Q. Or would you like to take a</p> <p>23 moment and read it yourself?</p> <p>24 A. No.</p> <p>25 Q. Okay. Now, is it your opinion</p>

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<p style="text-align: right;">Page 238</p> <p>1 that the nucleophilic sulfur which DMSO</p> <p>2 contains interacts in any way whatsoever with</p> <p>3 the mineral talc?</p> <p>4 A. I'm sorry, I missed the first</p> <p>5 part of the question.</p> <p>6 Q. Is it your opinion that the</p> <p>7 nucleophilic sulfur, which they describe</p> <p>8 here, which DMSO contains, interacts in any</p> <p>9 way whatsoever with the mineral talc?</p> <p>10 A. I have no knowledge of the</p> <p>11 interaction of DMSO with the mineral talc.</p> <p>12 Q. Do you -- what objective</p> <p>13 evidence do you have that shows that talcum</p> <p>14 powder is rendered unstable in DMSO by this</p> <p>15 nucleophilic sulfur?</p> <p>16 A. None.</p> <p>17 MS. MILLER: Objection.</p> <p>18 THE WITNESS: Sorry.</p> <p>19 MS. MILLER: Are we ready for a</p> <p>20 break?</p> <p>21 MR. RESTAINO: Ready for a</p> <p>22 break?</p> <p>23 MS. MILLER: I am.</p> <p>24 THE WITNESS: Sure.</p> <p>25 VIDEOGRAPHER: Off the record</p>	<p style="text-align: right;">Page 240</p> <p>1 MS. MILLER: It's starts on</p> <p>2 3913, and what page do you want?</p> <p>3 MR. RESTAINO: 3915.</p> <p>4 MS. MILLER: So maybe we could</p> <p>5 guess that it's around -- and we're</p> <p>6 not supposed to guess today.</p> <p>7 MR. RESTAINO: I know, but they</p> <p>8 got page number -- well, let's see if</p> <p>9 they have the page number up above.</p> <p>10 THE WITNESS: Well, the problem</p> <p>11 is this is the public access version</p> <p>12 as opposed to the Cancer Research</p> <p>13 version, and so the page numbers are</p> <p>14 going to just be 1, 2, 3, 4 in the</p> <p>15 public access version.</p> <p>16 MS. MILLER: But if we guess,</p> <p>17 13, 14, 15, it should be page 3.</p> <p>18 What words are you looking for?</p> <p>19 QUESTIONS BY MR. RESTAINO:</p> <p>20 Q. "Discussion" is on the lower</p> <p>21 right-hand side.</p> <p>22 A. We can find the discussion</p> <p>23 section if that's what we're doing. It's</p> <p>24 going to be at the end.</p> <p>25 Q. Yeah, I apologize. I actually</p>
<p style="text-align: right;">Page 239</p> <p>1 at 2:25 p.m.</p> <p>2 (Off the record at 2:25 p.m.)</p> <p>3 VIDEOGRAPHER: We are back on</p> <p>4 the record at 2:38 p.m.</p> <p>5 QUESTIONS BY MR. RESTAINO:</p> <p>6 Q. Welcome back, Doctor.</p> <p>7 Before we broke, we were</p> <p>8 discussing the Hall paper which was your</p> <p>9 reference.</p> <p>10 Would you be kind enough, sir,</p> <p>11 to turn to page -- to -- give me one second.</p> <p>12 I apologize. I wrote down the wrong page</p> <p>13 number.</p> <p>14 Page 3919. And I apologize for</p> <p>15 the delay. And --</p> <p>16 A. 39 -- in Hall, et al.?</p> <p>17 Q. Yeah.</p> <p>18 A. I'm sorry, I've got pages 1, 2,</p> <p>19 3.</p> <p>20 Q. And that's exactly what I'm</p> <p>21 seeing also.</p> <p>22 MS. MILLER: What's the issue?</p> <p>23 What do you want?</p> <p>24 THE WITNESS: It's just a page</p> <p>25 number issue.</p>	<p style="text-align: right;">Page 241</p> <p>1 have two different versions. The printed</p> <p>2 version and my electronic version are</p> <p>3 different. My apologies.</p> <p>4 A. All right. Discussion is</p> <p>5 always at the end.</p> <p>6 Q. It appears to be page 9.</p> <p>7 A. Yes.</p> <p>8 Q. Okay. Down below, Discussion.</p> <p>9 "We have demonstrated here the profound</p> <p>10 effects of DMSO on platinum drugs and</p> <p>11 complexes that contain monodentate ligands. "</p> <p>12 Did I read that correctly?</p> <p>13 A. You did.</p> <p>14 Q. Does talc powder contain one of</p> <p>15 those monodentate ligands?</p> <p>16 A. I don't know.</p> <p>17 Q. The bottom, last sentence of --</p> <p>18 in your expert report now on page 4, we were</p> <p>19 discussing the use of DMSO as a solvent in A.</p> <p>20 Do you see that, sir?</p> <p>21 Sir, I'm on page 4.</p> <p>22 A. "Dr. Saed's failure," et</p> <p>23 cetera?</p> <p>24 Q. Yes. "Dr. Saed's failure to</p> <p>25 evaluate this possibility renders most of his</p>

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<p style="text-align: right;">Page 242</p> <p>1 results, open paren, those involving exposure 2 of cells to talc, close paren, unreliable." 3 Did I read that correctly? 4 A. Yes. 5 Q. And your one reference for this 6 entire paragraph is the Hall paper which has 7 to do with platinum-based metals and the 8 dissolution of the ligand by DMSO and has 9 nothing to do with talc; is that correct? 10 A. So far as I know. 11 I would add that over the 12 course of my career in conducting similar 13 studies, before having read this paper rather 14 recently and conducting studies with cells 15 and platinum, I, too, perform lots of 16 experiments, in fact, using DMSO as a solvent 17 for one or another compound that I was 18 treating cells with. 19 And I observed over the years 20 that after a period of time, even hours, a 21 clear solution containing a treatment 22 compound, if you will, or an experimental 23 compound, in DMSO frequently leads to the 24 clear solution turning brown over a short 25 period of time, which is consistent with the</p>	<p style="text-align: right;">Page 244</p> <p>1 QUESTIONS BY MR. RESTAINO: 2 Q. Inasmuch as the Hall paper 3 deals with metal-based, platinum-based 4 chemotherapy agents which are dissolved by 5 DMSO by losing the ligand, which has nothing 6 to do with talc, would you agree that your 7 opinion in this regard is unreliable, as you 8 describe Dr. Saed's opinion? 9 A. Well, first of all -- and I'm 10 just going to read the question. I'm sorry. 11 I believe earlier I suggested 12 that at least some of the elements that 13 constitute talc are, in fact, metals, e.g., 14 silica. So I don't think the whole 15 metal-based argument for why this is, out of 16 hand, irrelevant is valid. 17 I don't think the fact that 18 this is a chemotherapeutic agent has anything 19 to do with the argument. It just happens to 20 be a chemotherapeutic agent. It could be any 21 other chemical used to test any other 22 hypothesis about any other biological 23 phenomenon. 24 And so I think the essence of 25 your argument here, and I'm starting to lose</p>
<p style="text-align: right;">Page 243</p> <p>1 characterization of dimethylsulfoxide as a 2 chemical oxidant. 3 And just based on personal 4 experience, it was my inference from watching 5 experimental agents turn brown over a period 6 of hours, certainly days, and having to throw 7 out the solution and then start over again 8 with fresh DMSO and fresh chemical, that the 9 agent that I was testing was being chemically 10 modified. 11 Q. Okay. 12 A. It's a personal anecdote. 13 Q. Okay. And then in addition to 14 that, Doctor, inasmuch as the Hall paper 15 deals with metal-based, platinum-based 16 chemotherapy agents with ligands and CMSO 17 {sic}, is your failure to evaluate this paper 18 as it relates to the use of DMSO by Dr. Saed 19 render your opinions in this regard 20 unreliable? 21 MS. MILLER: Objection. 22 THE WITNESS: Sorry, I just 23 couldn't follow the sentence. 24 MS. MILLER: Yeah, I couldn't 25 either.</p>	<p style="text-align: right;">Page 245</p> <p>1 it because it's going up the screen, about 2 rendering my opinion -- 3 MS. MILLER: I can stop it. 4 THE WITNESS: -- about 5 rendering my opinion obsolete or 6 irrelevant is off target. 7 QUESTIONS BY MR. RESTAINO: 8 Q. Okay. Let's go down to the 9 bottom of page 4, determination of talc 10 dosage. And I'm sorry, page 4 of your expert 11 report. And we can put Hall to the side. 12 And is your opinion that 13 "Dr. Saed used a very highly concentrated 14 talc solution, hyphen, 500 milligrams of talc 15 per 10 milliliter of DMSO, with reference 8. 16 He then applied relatively enormous doses of 17 talc, hyphen, from 5 to 100 micrograms per 18 milliliter, directly to the treated cells." 19 Did I read that correctly? 20 A. Yes. 21 Q. 500 milligrams of talc per 22 10 milliliters, that's 50 milligrams per 23 milliliter, agreed? 24 A. Agree. 25 Q. Do you know what the usual and</p>



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<p style="text-align: right;">Page 246</p> <p>1 customary dissolution dose of talcum powder 2 is when used for pleurodesis? 3 A. It must be extraordinarily high 4 based on the physiologic result that they're 5 attempting to achieve -- 6 Q. How about -- 7 A. -- which is massive fibrosis in 8 the closing off of the cavity between the 9 chest wall and the lung. 10 Q. Would it surprise you that it's 11 5 grams dissolved in 50 to 100 millimeters of 12 normal saline? 13 A. It wouldn't surprise me at all. 14 Q. And 5 grams equates to 15 5,000 milligrams? 16 A. I'm sorry, could we back up a 17 minute? I would just like to be clear about 18 what you were stating about the solvent 19 that's used in pleurodesis. I believe you 20 said normal saline. 21 Q. Correct. 22 NS. Does that make sense? 23 A. Well, I'm reading normal 24 saline. 25 Q. Okay.</p>	<p style="text-align: right;">Page 248</p> <p>1 Dr. Saed's notebook where they actually 2 played around with dissolving talc in a 3 slurry at one point. 4 Q. Play around -- 5 A. Freeze -- I'm sorry, that's an 6 inappropriate term. I'm sure he's a serious 7 man and doesn't play around in the lab. 8 They -- they experimented with 9 the process of dissolving talc in an aqueous 10 solution as a slurry, and for reasons that 11 aren't clear to me, as is the case for most 12 of what goes on in his laboratory notebooks, 13 they abandoned that approach and chose to use 14 DMSO, which completely dissolved the talc. 15 Q. And you don't know why they did 16 that, though? 17 A. Well, no, I can't -- I can't 18 infer what they may have been thinking. 19 Q. Do you know if the dose used by 20 Dr. Saed is equivalent to the doses reported 21 as used by others that have published, 22 including, for example, Dr. Shukla, 23 Dr. Akhtar twice? 24 A. That's a good question. I did 25 look at those papers, and I did look at the</p>
<p style="text-align: right;">Page 247</p> <p>1 A. But, no, I think it would have 2 been fantastic. 3 And I know you disagree with 4 the retrospectoscope, but my whole point was 5 we could avoided all of these -- could have 6 avoided all of these uncertainties in this 7 experimental design had he used an inert 8 solvent such as normal saline to dissolve the 9 talc. 10 Q. Does talc dissolve in normal 11 saline? 12 A. Apparently in pleurodesis it 13 seems to, based on what you just read. 14 Q. So you don't know what is 15 injected during pleurodesis? 16 A. Talc. 17 Q. Do you know what form, what -- 18 strike that. 19 What -- do you know that it's a 20 slurry that's involved? 21 A. Yes. 22 Q. Okay. Is a slurry different 23 from normal saline? 24 A. Yes. 25 And I'm also familiar with</p>	<p style="text-align: right;">Page 249</p> <p>1 doses, and the dose range tended to be much 2 lower in those papers. 3 Q. Can you give us the dose range 4 in those papers versus what Dr. Saed used? 5 A. Roughly. 6 MS. MILLER: Objection. 7 THE WITNESS: Yeah, I'm not 8 going to speculate without the papers 9 in front of me. I'd be happy to read 10 the doses from the X axis if you've 11 got the papers on hand. 12 QUESTIONS BY MR. RESTAINO: 13 Q. Okay. Is it your opinion that 14 there was a substantive difference in the 15 doses -- 16 A. Absolutely. 17 Q. -- used? 18 And you're relying upon those 19 papers and Dr. Saed's published paper for 20 that? 21 MS. MILLER: Objection. 22 THE WITNESS: Well, I'm relying 23 on more than that. That's part of the 24 equation. Part of the calculus, if 25 you will.</p>



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<p style="text-align: right;">Page 250</p> <p>1 QUESTIONS BY MR. RESTAINO:  2 Q. Okay.  3 A. I'm also relying on doses that  4 have been used in, for example, the Hamilton  5 study.  6 Q. Okay.  7 A. Where he injected approximately  8 10 milligrams into an entire rat ovary, which  9 compared -- which by my conservative estimate  10 is likely to contain tens of millions of  11 cells. And in this particular case, he's  12 treating 100-millimeter square dishes  13 containing a couple hundred thousand cells.  14 And the back-of-the-envelope  15 calculation is that he's using -- again, in  16 my estimation, using, granted, a subjective  17 term, a relatively massive dose.  18 Q. He's actually using -- when he  19 used the 5 micrograms per milliliter, he's  20 using 0.005 percent of that which is injected  21 during pleurodesis; is that correct?  22 MS. MILLER: Objection.  23 THE WITNESS: Well, I'll take  24 your arithmetic at face value.  25 I think it's important to</p>	<p style="text-align: right;">Page 252</p> <p>1 Q. Yes.  2 A. Correct.  3 Q. Okay. So when it's injected  4 there, it's going into a very small space to  5 begin with before it's distributed throughout  6 the pleural cavity, correct?  7 A. Yes, just as when one takes a  8 Pipetman and pipettes -- a certain amount of  9 DMSO containing talc onto a 100-millimeter  10 dish, and then swirling the dish around to  11 distribute the talc over the cells, it's a  12 similar concept.  13 Q. So in that -- what he's put  14 into his dish as compared to where that  15 needle goes, he's injected 0.0005 percent of  16 what's injected into a living human being?  17 A. Which is still a massive dose  18 based on the number of cells being treated,  19 relatively speaking.  20 You're trying to use arithmetic  21 to conflate the point I'm making.  22 Q. Okay.  23 A. And the number of cells that  24 are being treated and the space that's -- the  25 space that's receiving the amount of</p>
<p style="text-align: right;">Page 251</p> <p>1 consider the size of the pleural  2 cavity that is injected with talc  3 during the process of pleurodesis,  4 which as far as I can tell is used  5 primarily to prevent pleural effusions  6 or perhaps pneumothorax in patients  7 with lung cancer, by closing off what  8 is arguably a very large physical  9 space containing perhaps billions of  10 cells.  11 And Dr. Saed's experiments,  12 again, were performed in a  13 100-millimeter-squared petri dish,  14 which is roughly that large, with a  15 nonconfluent modulator of cells,  16 roughly 100,000, 200,000 perhaps. And  17 we're talking about logarithmic  18 differences of scale in terms of  19 pleurodesis versus the in vitro  20 experiments.  21 QUESTIONS BY MR. RESTAINO:  22 Q. When the pleurodesis is  23 injected, it's injected using a large bore,  24 typically an 18-gauge needle, correct?  25 A. An 18-gauge needle.</p>	<p style="text-align: right;">Page 253</p> <p>1 physiologic, biologic space that's receiving  2 the talc that's being either injected or  3 pipetted into a dish, injected into a human  4 or pipetted into a petri dish.  5 Q. Okay. Continue on with  6 determination of talc dose. You write,  7 second line from the bottom, "Indeed, the  8 evidence that any" -- and you bold "any" and  9 italicize "any" -- "talc can reach the  10 ovaries from external perineal use is weak."  11 Did I read that correctly?  12 A. You did.  13 Q. And are you an expert in the  14 migration of external particles from the  15 environment to the vagina to the fallopian  16 tubes and/or ovaries?  17 A. No. Sorry.  18 MS. MILLER: Objection. I --  19 that was an objectionable question.  20 Please give me time to object.  21 THE WITNESS: So noted.  22 MS. MILLER: Don't rush.  23 QUESTIONS BY MR. RESTAINO:  24 Q. And you have a reference for  25 that, which is the 2010 IARC monograph on</p>

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<p>1 "Evaluation of carcinogenic risks to human, 2 Volume 93: Carbon black, titanium dioxide, 3 and talc 411," correct? 4 MS. MILLER: Objection. He has 5 three references, if I'm reading the 6 right footnote. 7 MR. RESTAINO: And I'm sorry, 8 I -- no, indeed, I'm reading from the 9 sentence, Jessica, "The evidence of 10 any talc can reach the ovaries from 11 external perineal use" -- 12 MS. MILLER: Are we looking at 13 footnote 10? Maybe I misunderstood 14 you, but it sounded like you were 15 saying there was one reference. 16 MR. RESTAINO: Oh, I'm just 17 reading the first one, the IARC one. 18 MS. MILLER: You said you have 19 a reference. 20 MR. RESTAINO: They're on the 21 same page. 22 QUESTIONS BY MR. RESTAINO: 23 Q. Do you see that, sir? 24 A. I do. 25 Q. And then turning to the next</p>	<p>1 capable of just saying "objection"? 2 You know that is the Federal 3 Rules, which is why we went to school 4 and we took all those classes. 5 MS. SHARKO: Okay. Let's just 6 move on. 7 (Boyd Exhibit 17 marked for 8 identification.) 9 QUESTIONS BY MR. RESTAINO: 10 Q. Doctor, I've now marked as Boyd 11 17 an article by McDonald, et al., or 12 McDonald, et al. And I'll represent to you 13 that this paper was published in March 2019. 14 Have you seen this paper 15 before? 16 A. I have. 17 Q. Okay. If you would turn to 18 page 12, if I'm correct, there should be a 19 section there in the upper left called 20 Discussion. 21 A. It's there. 22 Q. In the second paragraph they 23 write, "Talc, when applied to the perineum, 24 is believed to migrate to the upper genital 25 tract, passing through the open tract to the</p>
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<p>1 page, you have a 1971 reference by Henderson, 2 et al., correct? 3 A. Correct. 4 Q. And then you have a 1996 5 reference by Heller, correct? 6 A. Correct. 7 Q. Have you seen any other papers 8 that have been published more recently 9 regarding migration of talc powder -- of 10 particles throughout the female reproductive 11 tract? 12 MS. MILLER: Objection. 13 Can you ask a better question 14 there? 15 Are you asking about talc 16 powders? Are you asking about 17 particles and -- 18 MR. RESTAINO: Talc powder and 19 particles. 20 MS. MILLER: Both? 21 MR. RESTAINO: Both. 22 MS. MILLER: Okay. That's a 23 new question. 24 MR. RESTAINO: Can't you just 25 say "objection"? Truly, are you</p>	<p>1 fallopian tubes and eventually reaching the 2 ovaries." References 11 and 16. 3 Did I read that correctly? 4 A. Yes, you did. 5 Can we dissect references 11 6 through 16? 7 Q. And I was going to suggest to 8 you, would you like to look at references 11 9 and 16? 10 A. Yes. 11 Q. Okay. Reference 11 is by 12 Cramer, et al., "The association between talc 13 use and ovarian cancer: A retrospective 14 case-control study in two US states," 15 published in Epidemiology in 2016; is that 16 correct? 17 A. You have read it correctly. 18 Q. And we discussed earlier 19 Dr. Daniel Cramer, the physician, 20 epidemiologist, correct? 21 A. And gynecologist, correct. 22 Q. And then reference 16 is the 23 Penninkilampi and Eslick paper, "Perineal 24 talc use and ovarian cancer: A systematic 25 review and meta-analysis," also published in</p>

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<p style="text-align: right;">Page 258</p> <p>1 Epidemiology. 2 This was in 2018; is that 3 correct? 4 A. I'm sorry, can we go back to 5 the original sentence? I believe you're 6 mixing references here. I'm sorry. 7 MS. MILLER: I'm afraid to 8 speak because you don't like me to say 9 anything more than objection, but -- 10 THE WITNESS: 11 and 16. 11 Henderson is 16, "Talc and carcinoma 12 of the ovary and cervix." 13 MR. RESTAINO: Oh, my mistake. 14 I'm sorry. 15 QUESTIONS BY MR. RESTAINO: 16 Q. And so reference 16 is the 17 Henderson study, correct? 18 A. Correct. 19 Q. Now, you reference the article, 20 the three references there, for the evidence 21 that talc can reach the ovaries from external 22 perineal use is weak; is that correct? 23 A. Well, if I recall, as I read 24 the articles, the first of the three 25 references that I cited I quote directly.</p>	<p style="text-align: right;">Page 260</p> <p>1 MR. RESTAINO: No. Just wonder 2 if he recalled reading that. 3 QUESTIONS BY MR. RESTAINO: 4 Q. Do you know what retrograde 5 transportation is as used with the female 6 reproductive tract? 7 A. I can infer that it would mean 8 stuff going north. 9 Q. Okay. And are you an expert -- 10 A. In stuff -- 11 Q. -- in the female reproductive 12 tract with stuff going north? 13 MS. MILLER: Objection. 14 THE WITNESS: No. 15 QUESTIONS BY MR. RESTAINO: 16 Q. Would you defer to a 17 gynecologist and a gynecologic oncologist 18 who -- for their -- their opinions on stuff 19 going north? 20 MS. MILLER: Objection. 21 THE WITNESS: I wouldn't 22 refer -- I'm sorry. I wouldn't defer 23 to people. I would defer to 24 literature and evidence. 25 MS. SHARKO: Ms. Thompson,</p>
<p style="text-align: right;">Page 259</p> <p>1 That is the IARC paper, or the monograph, if 2 you will, describing the evidence as weak, 3 and further animal studies showed no evidence 4 of retrograde transport of talc to the 5 ovaries. 6 And then we could further 7 dissect the actual data in the Henderson and 8 Heller papers, if you'd like, in terms of 9 what they actually found and whether it has 10 anything at all to do with talc getting from 11 the perineum to the ovaries. 12 Q. Do you recall in the -- your 13 review of the IARC monograph that they also 14 stated that in women with impaired clearance 15 function evidence of retrograde transport was 16 found? 17 A. No. 18 Q. Do you know -- 19 A. I remember what I wrote in my 20 footnote because it's there. 21 Q. Do you know -- 22 A. I don't remember anything in 23 the paper except what I've written here. 24 MS. MILLER: Do you want to 25 show him the papers?</p>	<p style="text-align: right;">Page 261</p> <p>1 didn't you say there was a no laughing 2 rule during depositions? 3 MS. THOMPSON: Well, Jessica is 4 laughing. She has been a good part of 5 the day. 6 MS. SHARKO: Not that I saw, 7 and I'm sitting right next to her. 8 MS. THOMPSON: And you'll have 9 to agree that things going -- stuff 10 going north is kind of funny, isn't 11 it, as a description? 12 That is all. It wasn't meant 13 to be derogatory in any way. 14 MR. RESTAINO: Can we move on? 15 MS. THOMPSON: Sorry, yes. 16 QUESTIONS BY MR. RESTAINO: 17 Q. Can we go to your expert report 18 at the top of page 5? And I apologize for 19 giggling. 20 A. No apology necessary. 21 Q. You write -- down toward the 22 bottom section of the top paragraph, you 23 start on the right, after reference 13, "But 24 the logical conclusion of this argument." 25 Do you see that, sir?</p>

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<p style="text-align: right;">Page 262</p> <p>1 A. Yes.</p> <p>2 Q. "But the logical conclusion of</p> <p>3 this argument would be that the same</p> <p>4 mechanisms of expulsion of talc from the</p> <p>5 areas of the female reproductive tract distal</p> <p>6 to the ovaries, open paren, vagina, cervix,</p> <p>7 uterus, fallopian tubes, close paren, should</p> <p>8 also prevent talc from otherwise migrating,</p> <p>9 hyphen, like a salmon upstream, hyphen,</p> <p>10 through this wash of bodily fluids,</p> <p>11 eventually reaching the ovaries."</p> <p>12 Is that correct?</p> <p>13 A. That's correct, and I apologize</p> <p>14 for using analogies that aren't entirely</p> <p>15 anatomical.</p> <p>16 Q. However, you don't have a</p> <p>17 reference for this opinion, correct?</p> <p>18 A. Well, if we could back up a</p> <p>19 little bit, I think it's useful to take this</p> <p>20 particular sentence in context.</p> <p>21 Q. In the context of the previous</p> <p>22 references?</p> <p>23 A. No, in the context of this</p> <p>24 entire paragraph.</p> <p>25 Q. Okay.</p>	<p style="text-align: right;">Page 264</p> <p>1 salmon upstream through the wash of bodily</p> <p>2 fluids."</p> <p>3 So in other words, it's got to</p> <p>4 be one way or the other. You can't argue</p> <p>5 that stuff is being constantly flushed out</p> <p>6 while suggesting that stuff is at the same</p> <p>7 time -- in other words, south and north at</p> <p>8 the same time through the same organ system.</p> <p>9 Q. Isn't it true that on a monthly</p> <p>10 basis when a woman is menstruating that the</p> <p>11 endometrium is sloughed off?</p> <p>12 A. It is true.</p> <p>13 Q. Is the internal aspect of the</p> <p>14 ovary sloughed off?</p> <p>15 A. What's the internal aspect of</p> <p>16 the ovary?</p> <p>17 Q. In any internal -- internal</p> <p>18 cellular components of the ovary, are they</p> <p>19 sloughed off during menstruation?</p> <p>20 MS. MILLER: Objection.</p> <p>21 THE WITNESS: You'd have to ask</p> <p>22 a more specific question than that.</p> <p>23 I'm sorry.</p> <p>24 QUESTIONS BY MR. RESTAINO:</p> <p>25 Q. Does -- during menstruation,</p>
<p style="text-align: right;">Page 263</p> <p>1 A. Could I read it?</p> <p>2 Q. Of course, sir.</p> <p>3 A. "In attempting to explain why</p> <p>4 talc would not produce inflammation and</p> <p>5 cancer in the intervening areas of the female</p> <p>6 reproductive anatomy, for example, Dr. Saed</p> <p>7 repeatedly referred to the wash,</p> <p>8 quote/unquote, of bodily fluids that would</p> <p>9 expel particulate matter," and then I</p> <p>10 referenced his deposition transcript.</p> <p>11 "Dr. Saed contrasted this protective</p> <p>12 mechanism to that of the ovaries, which he</p> <p>13 claims have no mechanism for removing foreign</p> <p>14 particles." Again, deposition transcript.</p> <p>15 "But the logical conclusion of</p> <p>16 this argument" -- and this is where I think</p> <p>17 context is important, so he's -- he's</p> <p>18 referring to the wash of bodily fluids that</p> <p>19 would expel particulate matter. "But the</p> <p>20 logical conclusion of this argument would be</p> <p>21 that the same mechanisms of expulsion of talc</p> <p>22 from areas of the female reproductive tract</p> <p>23 below the ovaries, i.e., vagina, cervix,</p> <p>24 uterus and fallopian tubes, should also</p> <p>25 prevent talc from otherwise migrating like a</p>	<p style="text-align: right;">Page 265</p> <p>1 does any part of the ovary, other than the</p> <p>2 egg that's bursting through, does any part</p> <p>3 of -- of the ovarian tissue slough off during</p> <p>4 menstruation?</p> <p>5 MS. MILLER: Objection.</p> <p>6 THE WITNESS: If you could ask</p> <p>7 a more specific question, I'd be happy</p> <p>8 to answer it.</p> <p>9 For example, what part of the</p> <p>10 ovary?</p> <p>11 QUESTIONS BY MR. RESTAINO:</p> <p>12 Q. Regarding the effect of</p> <p>13 menstruation on an ovary, on a monthly basis</p> <p>14 in a woman, would you defer to a</p> <p>15 gynecologist?</p> <p>16 A. Again, I generally don't defer</p> <p>17 to people or particular professions. I defer</p> <p>18 to textbooks and scientific literature to</p> <p>19 form opinions on anything that I'm rendering.</p> <p>20 Q. Okay. And do you render</p> <p>21 opinions on whether or not tissue is flushed</p> <p>22 from the ovary during menstruation?</p> <p>23 A. I'm not now because I just</p> <p>24 simply don't understand the question.</p> <p>25 Q. Okay. Are you familiar with</p>

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<p style="text-align: right;">Page 266</p> <p>1 any studies documenting that dead sperm and 2 inanimate sperm particles are efficiently 3 transported upward through the -- excuse me, 4 through the uterus and tubules? 5 MS. MILLER: Objection. 6 THE WITNESS: I'm familiar with 7 multiple allusions to 8 Dr. Clarke-Pearson's expert report 9 and/or deposition where this example 10 has been raised multiple times in 11 reading defendants' deposition 12 transcripts. So I assume that such 13 literature exists, but I've only read 14 it indirectly through plaintiffs' 15 attorneys' questions and defendants' 16 deposition transcripts. 17 QUESTIONS BY MR. RESTAINO: 18 Q. Of one, Dr. Clarke-Pearson. 19 That's the only one you've read? 20 MS. MILLER: Objection. That's 21 not what he said. 22 THE WITNESS: That's not what I 23 said. 24 QUESTIONS BY MR. RESTAINO: 25 Q. Well, regarding on the</p>	<p style="text-align: right;">Page 268</p> <p>1 transcripts of several defendant expert 2 witnesses versus the plaintiff expert 3 witnesses, is that a form of confirmation 4 bias? 5 MS. MILLER: Objection. 6 THE WITNESS: I think -- I'm 7 sorry for laughing, but that's an 8 unusually creative question. 9 I simply don't know how to 10 answer that. I'm sorry. 11 QUESTIONS BY MR. RESTAINO: 12 Q. Okay. Now, you've reviewed the 13 paper by Saed, et al., because Dr. Saed is 14 not the sole author of the paper "Molecular 15 Basis Supporting the Association with Talcum 16 Powder Use with Increased Risk of Ovarian 17 Cancer." Is that correct? 18 MS. MILLER: Objection. 19 THE WITNESS: Two things -- 20 noting objection. 21 First of all, it's Fletcher, et 22 al., and second -- 23 MS. MILLER: That was the 24 objection. 25 THE WITNESS: -- could we look</p>
<p style="text-align: right;">Page 267</p> <p>1 plaintiff side, what other plaintiff 2 gynecological oncology deposition did you 3 read? 4 MS. MILLER: Huh? Objection. 5 THE WITNESS: I read -- 6 MS. MILLER: Wait a minute. 7 Objection. 8 You don't want me to say 9 anything further, but he never said 10 anything about reading Dr. -- I think 11 you just need to read his testimony 12 and ask your question again. 13 QUESTIONS BY MR. RESTAINO: 14 Q. Doctor, did you read Clarke -- 15 Dr. Clarke-Pearson's expert report and his 16 deposition transcript? 17 A. I skimmed it. I've read much 18 more carefully the deposition transcripts of 19 several defendants' expert witnesses where 20 they are consistently asked on multiple 21 occasions by plaintiffs' lawyers as to 22 whether they're familiar with 23 Dr. Clarke-Pearson's testimony that dead 24 sperm can migrate north. 25 Q. So in reading the deposition</p>	<p style="text-align: right;">Page 269</p> <p>1 at the paper? 2 QUESTIONS BY MR. RESTAINO: 3 Q. Yes. And I've marked the paper 4 as 18. 5 A. Are we done with McDonald? 6 Q. With who? 7 A. McDonald? 8 Q. Yes, sir. 9 A. Thank you. 10 (Boyd Exhibit 18 marked for 11 identification.) 12 QUESTIONS BY MR. RESTAINO: 13 Q. So what we've been as calling 14 Dr. Saed's paper, or Fletcher, et al., does 15 have multiple coauthors, correct? 16 A. Does indeed. 17 Q. And do you know any of these 18 authors? 19 A. No. 20 Q. And the paper itself was 21 submitted -- originally submitted to 22 Gynecologic Oncology, correct? 23 A. It's my understanding. 24 Q. And there were two peer 25 reviewers that took a look at it, or at least</p>

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<p style="text-align: right;">Page 270</p> <p>1 two that we know of?</p> <p>2 A. The latter. For the record,</p> <p>3 there were at least two that rendered an</p> <p>4 opinion, yes.</p> <p>5 Q. Okay. And would you agree that</p> <p>6 in the typical peer-review process of a</p> <p>7 medical or scientific paper, reviewers with</p> <p>8 expertise in the subjective -- in the subject</p> <p>9 matter of the submitted manuscript are</p> <p>10 selected to conduct a review?</p> <p>11 A. That's certainly the goal. It</p> <p>12 doesn't always happen, but that's -- that's</p> <p>13 clearly the goal of peer review.</p> <p>14 Q. Okay.</p> <p>15 A. Obviously with millions of</p> <p>16 papers being published and a finite number of</p> <p>17 journals, the expertise and the content don't</p> <p>18 always tick and tie, but that's certainly the</p> <p>19 goal of peer review, yes.</p> <p>20 Q. Is it reasonable to conclude</p> <p>21 that the two peer reviewers for Gynecologic</p> <p>22 Oncology were experts in the subject matter</p> <p>23 of the Fletcher, et al., paper?</p> <p>24 MS. MILLER: Objection. Calls</p> <p>25 for speculation.</p>	<p style="text-align: right;">Page 272</p> <p>1 you recall that.</p> <p>2 A. Well, that's an interesting</p> <p>3 question on several accounts. Yes, I did</p> <p>4 read it, but I'd like to have the opportunity</p> <p>5 to comment on the content of the entire</p> <p>6 letter as opposed to some sentences extracted</p> <p>7 out of context, perhaps.</p> <p>8 Q. Okay.</p> <p>9 A. So if we could share the</p> <p>10 letter, that would be very useful.</p> <p>11 Q. I will do that.</p> <p>12 A. Thank you.</p> <p>13 Q. Have you ever had a paper</p> <p>14 submitted to a journal and have it rejected?</p> <p>15 A. Many times.</p> <p>16 Q. So the papers that you've</p> <p>17 had -- that you've submitted that have been</p> <p>18 rejected many times, were they flawed papers?</p> <p>19 A. That's a very vague term,</p> <p>20 "subjective."</p> <p>21 Q. Were they papers that were</p> <p>22 subsequently published by another journal?</p> <p>23 A. I would say, again, there's a</p> <p>24 fine line between guessing and estimating.</p> <p>25 First, let's start with the</p>
<p style="text-align: right;">Page 271</p> <p>1 THE WITNESS: I have no idea</p> <p>2 what the expertise of the anonymous</p> <p>3 reviewers of the Fletcher, et al.,</p> <p>4 paper submitted to Gynecologic</p> <p>5 Oncology is -- are.</p> <p>6 I'm sorry. I'm losing track of</p> <p>7 my own sentence.</p> <p>8 QUESTIONS BY MR. RESTAINO:</p> <p>9 Q. Did you read the letter from</p> <p>10 the editor of Gynecologic Oncology to</p> <p>11 Dr. Saed regarding that the journal,</p> <p>12 Gynecologic Oncology, was currently only</p> <p>13 accepting less than 20 percent of the</p> <p>14 manuscripts submitted?</p> <p>15 A. I did.</p> <p>16 And could we have a copy of the</p> <p>17 letter if we're going to discuss the letter?</p> <p>18 Q. If we're going to discuss the</p> <p>19 letter, sure.</p> <p>20 A. Sounds like we are. I'm</p> <p>21 just -- I'm sorry.</p> <p>22 Q. Yeah, I think we're just coming</p> <p>23 to it. I'm not going to get into the details</p> <p>24 of it. I just want to know at this point if</p> <p>25 you've read it and you've reviewed that, if</p>	<p style="text-align: right;">Page 273</p> <p>1 reality of publishing papers.</p> <p>2 In my 35-year experience of</p> <p>3 publishing papers and indeed serving as a</p> <p>4 peer reviewer for more than 40, 45 journals,</p> <p>5 and indeed with respect to Gynecologic</p> <p>6 Oncology in particular, having reviewed,</p> <p>7 conservatively, 150 papers for Gynecologic</p> <p>8 Oncology, having served on the editorial</p> <p>9 board of Gynecologic Oncology, and indeed</p> <p>10 having served as associate editor for</p> <p>11 Gynecologic Oncology, I can assure you that</p> <p>12 there are very few papers in science</p> <p>13 generally, and biomedical science generally,</p> <p>14 in the context of any journal that are</p> <p>15 accepted without revision on first</p> <p>16 submission.</p> <p>17 And so it's -- it's not only</p> <p>18 usual, it is in fact the norm, for a paper to</p> <p>19 receive constructive -- generally always</p> <p>20 constructive -- comments about how the paper</p> <p>21 could be improved based on the opinions of</p> <p>22 the presumptive expert reviewers.</p> <p>23 Q. And it's true, is it not, that</p> <p>24 Fletcher, et al., then submitted the paper to</p> <p>25 Reproductive Sciences?</p>



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<p style="text-align: right;">Page 274</p> <p>1 A. After they were disinvited to 2 submit a revised version to Gynecologic 3 Oncology, correct. 4 Q. Disinvited? 5 A. Yeah, again, could we see the 6 letter, please, so we don't have to guess 7 about what's boilerplate and what's actually 8 not boilerplate on a letter from the editor 9 from Gynecologic Oncology? 10 I've got quite a lot of 11 experience with the journal. 12 (Boyd Exhibit 19 marked for 13 identification.) 14 QUESTIONS BY MR. RESTAINO: 15 Q. I'll mark this as 19. 16 And this is what you've seen, 17 sir? 18 A. Yes. 19 Q. And the first page, you see 20 it's to Ghassan Saed with cc's, correct? 21 A. Yes. 22 Q. From Gynecologic Oncology, 23 correct? 24 A. Correct. 25 Q. And you see the first</p>	<p style="text-align: right;">Page 276</p> <p>1 says exactly the same thing, I can assure 2 you. It's a fact. 3 Q. Does that decrease the merit of 4 what they're saying in the letter? 5 A. No, I'm just helping you to 6 understand the letter. You're interested in 7 discussing the letter. 8 Q. Well, I understand letters from 9 editors and peer-reviewers, very much so. 10 A. Well, we're talking about a 11 specific letter from a specific journal in 12 this case, Gynecologic Oncology, and I'm not 13 sure if you're familiar with Gynecologic 14 Oncology or not. 15 Q. And while I've never submitted 16 a paper to this journal, can you sit there 17 and tell us today that this first paragraph 18 is the exact same paragraph that they send to 19 every paper that they don't accept, the 20 80 percent of which is submitted to them? 21 Can you sit here and say that 22 that paragraph is the exact same thing? 23 A. That are rejected outright; in 24 other words, on first submission, I can state 25 that as a fact.</p>
<p style="text-align: right;">Page 275</p> <p>1 paragraph: "Your paper, referenced above, 2 has now been reviewed by at least two experts 3 in the field and the editors. Based on the 4 reviewers' comments, we must inform you that 5 while your work is not without merit, we are 6 unable to accept your manuscript for 7 publication in Gynecologic Oncology. In the 8 last year, we have seen a significant 9 increase in the number of manuscripts 10 submitted to the journal and as a result, we 11 are now accepting less than 20 percent of the 12 manuscripts submitted to Gynecologic 13 Oncology." 14 Did I read that carefully? 15 A. I don't know, but you read it 16 correctly. 17 Q. I read it correctly? 18 A. Yes. 19 Q. Where in there does it say he 20 was disinvited? 21 A. We haven't gotten there yet. 22 First of all, the paragraph 23 that you just read, for any paper that's 24 rejected outright from Gynecologic Oncology, 25 this is boilerplate. Every single letter</p>	<p style="text-align: right;">Page 277</p> <p>1 Q. Okay. Now, do you know if this 2 paper was ultimately submitted to 3 Reproductive Sciences? 4 A. I'd like to move on with this 5 letter. I mean, you're -- to use a phrase 6 I've used -- cherry-picking pieces of the 7 letter and avoiding others that I think bear 8 on the veracity of the paper as the reviewer 9 saw it submitted to Gynecologic Oncology. 10 Q. I'm actually going to come back 11 to that, so I'd like to -- 12 A. Well, I hope so, because I 13 think it's important. 14 Q. Well, your attorney is going to 15 have a chance to ask you about it, as I said. 16 Okay? It's my turn -- 17 A. Well, you said you were going 18 to come back to it, but -- 19 Q. I may if we have time. Okay. 20 MS. MILLER: Again -- 21 THE WITNESS: For the record, 22 I'd like to continue on the topic of 23 this particular paper from this 24 particular journal because I think it 25 bears on the quality of the manuscript</p>

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<p style="text-align: right;">Page 278</p> <p>1 as the reviewers from Gynecologic 2 Oncology viewed it. 3 MR. RESTAINO: And if we have 4 time, I'm going to get back to it. I 5 have more questions about that letter. 6 THE WITNESS: Noted. 7 MS. MILLER: Are we done with 8 this exhibit? 9 MR. RESTAINO: Just for the 10 time being. I'm going to return to 11 it. 12 QUESTIONS BY MR. RESTAINO: 13 Q. Now, on the bottom of page 6 of 14 your expert report, you have a section 15 Inadequate Control Experiments. 16 Do you see that, sir? 17 A. Yes. 18 Q. And you write, "Dr. Saed's 19 studies do not adequately address his 20 hypothesis that there is a biological 21 mechanism linking exposure to talc, open 22 paren, a hydrated magnesium silicate compound 23 consisting of magnesium, silicon and oxygen, 24 hyphen, all of which are found at one or 25 another concentration in the human body and</p>	<p style="text-align: right;">Page 280</p> <p>1 case and research -- 2 MS. MILLER: I'm sorry. 3 THE WITNESS: It's quite all 4 right. 5 My point was that the talc 6 particle is generally considered to be 7 chemically inert, and I was perhaps 8 opining at length about inert stuff in 9 the body that constitutes talc. 10 But my point here, as I 11 intended it then and as I intend it 12 today, is that talc is an inert -- a 13 chemically inert particle and that 14 it's my opinion, as apparently it was 15 for the other investigators that we've 16 discussed most recently that perform 17 similar experiments in vitro treating 18 cells with talc and so forth, to use 19 other inert particles to control for 20 the effect -- the simple effect of 21 placing extraordinarily large amounts 22 of inert particles on cells in culture 23 in order to measure a biological 24 phenomenon. 25 So in other words, is it</p>
<p style="text-align: right;">Page 279</p> <p>1 are, in fact, considered, quote, essential 2 elements, close paren, to ovarian 3 carcinogenesis because Dr. Saed failed to 4 perform additional control experiments 5 designed to test whether other particulate 6 compounds, such as, for example, cornstarch, 7 open paren, a powdered carbohydrate derived 8 from the endosperm of corn kernels, close 9 paren, or a particulate compound more 10 chemically similar to talc, such as finely 11 ground beach sand, open paren, silicon 12 dioxide, close paren, produce the same 13 results." 14 Did I read that correctly? 15 A. I'll submit that you did. 16 Q. Okay. Now, when you say 17 that -- why in this paragraph did you add 18 that magnesium silicon and oxygen are 19 considered essential elements? 20 A. I honestly don't remember. 21 Q. Okay. 22 A. My point is I think that -- if 23 I recall when I was composing this probably 24 late at night, since that's when I did 25 essentially all of my work related to this</p>	<p style="text-align: right;">Page 281</p> <p>1 specific to talc or is it simply the 2 result of dumping a lot of powder 3 on -- or finely ground, you know, 4 titanium oxide or glass beads, for 5 example, I think one of the 6 investigators used. I think they were 7 a little more careful in their 8 scientific approach, which I think 9 speaks to Dr. Saed's thought process 10 in designing the appropriate control 11 experiments for the ones he described 12 in this paper. 13 QUESTIONS BY MR. RESTAINO: 14 Q. Hydrogen is an essential 15 element also, isn't it? 16 A. Yes. 17 Q. Because it was left out of your 18 essential elements here. 19 A. Again, I think I explained my 20 rationale for describing them as essential 21 elements, and that's certainly not the -- the 22 gist nor the crux of my -- of my criticism of 23 the experimental design. 24 Q. Wasn't your intent to indicate 25 to any reader of this paragraph that these</p>

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<p>1 elements, including magnesium, silicon, 2 oxygen and the left out hydrogen, are 3 essentially safe because they're essential 4 elements in our body? 5 A. It was my point to indicate 6 that talc is inert, chemically unreactive, 7 generally speaking. And I apologize if it 8 doesn't meet your standards for describing a 9 compound as chemically inert. 10 Q. Is it physiologically inert? 11 A. I believe it is. 12 Q. And what do you base that upon? 13 A. Chemically inert is 14 physiologically inert. I mean -- 15 Q. Okay. 16 A. -- the cells, the tissues of 17 the human body, is -- of the human body is -- 18 are you about to hand us something? 19 Q. Yes, sir. 20 MS. MILLER: Finish your 21 sentence. If you're done. 22 THE WITNESS: Chemically inert, 23 in my mind, suggests that a compound, 24 a chemical, does not spontaneously 25 react with anything, which of course</p>	<p>1 I just want to look at them with you. 2 And you've got magnesium there, 3 correct? 4 MS. MILLER: Objection. 5 What is this? 6 MR. RESTAINO: Chemical 7 structure. 8 THE WITNESS: Could we 9 stipulate -- 10 MS. MILLER: Is this a 11 chemistry test? 12 THE WITNESS: Could we 13 stipulate that we've got magnesium, 14 silicon, oxygen and hydrogen here and 15 both agree? 16 QUESTIONS BY MR. RESTAINO: 17 Q. Yes. 18 And would you agree that all 19 the essential elements that we have been 20 discussing are located in that compound? 21 A. Yes. 22 Q. Okay. The bottom of page 6 and 23 top of page 7 of your expert report. 24 After you've been discussing 25 various additional control experiments and</p>
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<p>1 would include anything that you 2 classify as physiological. 3 QUESTIONS BY MR. RESTAINO: 4 Q. Are hydrated magnesium 5 silicates inert? 6 A. Well, there are different forms 7 of hydrated magnesium silicates, I presume, 8 which is where you're going with this, and 9 I'm sure some of them aren't -- a good 10 example would be the difference between -- 11 let's make something up -- water, H<sub>2</sub>O, which 12 is oxygen and hydrogen, and hydrogen 13 peroxide, H<sub>2</sub>O<sub>2</sub>, which differ by a single 14 oxygen molecule, one being very inert, the 15 other being very reactive. 16 So I think it's very safe to 17 say even though I don't hold myself out as a 18 chemist, that there are very likely to be 19 other hydrated magnesium silicates that are 20 not inert. 21 (Boyd Exhibit 20 marked for 22 identification.) 23 QUESTIONS BY MR. RESTAINO: 24 Q. I've marked as Exhibit 20 25 "Chemical Structure of Essential Elements."</p>	<p>1 experiments of Dr. Saed, et al., could have 2 performed, you write, "Such experiments 3 testing the potential biological effects of 4 other particulate compounds like talc could 5 have been used to determine whether his 6 findings were driven by some quality that is 7 unique to talc or rather its particulate form 8 generally, the characteristics of which are 9 shared by many other compounds." 10 Did I read that correctly? 11 A. You did, and I opined on that 12 point extensively just literally a few 13 seconds ago. 14 Q. Yes. 15 Do you know if those 16 experiments are being planned by Dr. Saed? 17 A. How would I know what he's 18 planning to do? 19 Q. Well, you're criticizing saying 20 that he could have done a lot of other 21 studies, that he could have done in vivo 22 studies, that he could have done a lot more, 23 which is not the normal sequence of 24 scientific study. 25 But all I'm asking now is, do</p>

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<p style="text-align: right;">Page 286</p> <p>1 you know if he's doing those experiments as</p> <p>2 we sit here today?</p> <p>3 MS. MILLER: Objection.</p> <p>4 THE WITNESS: Is that a</p> <p>5 rhetorical question, sir?</p> <p>6 QUESTIONS BY MR. RESTAINO:</p> <p>7 Q. No. I'm just asking, do you</p> <p>8 know?</p> <p>9 A. I haven't spoken to Dr. Saed --</p> <p>10 Q. Okay.</p> <p>11 A. -- so I have no way of knowing</p> <p>12 what he's planning to do in the future.</p> <p>13 Q. But you've criticized him for</p> <p>14 not correlating his in vitro studies with</p> <p>15 some in vivo studies at this time, correct?</p> <p>16 MS. MILLER: Objection.</p> <p>17 THE WITNESS: I'm criticizing</p> <p>18 him for his studies, his laboratory</p> <p>19 notebook, his deposition, his expert</p> <p>20 report, all the things that I've seen.</p> <p>21 Obviously I can't criticize him</p> <p>22 for things that he may or may not do</p> <p>23 in the future. I think that's kind</p> <p>24 of, again, I'm sorry, a silly</p> <p>25 question.</p>	<p style="text-align: right;">Page 288</p> <p>1 study.</p> <p>2 A. So we're switching gears here</p> <p>3 and going from a ostensible carcinogenesis</p> <p>4 study to a therapeutic study?</p> <p>5 Q. Yes.</p> <p>6 A. Okay?</p> <p>7 Q. Yes.</p> <p>8 A. Please proceed.</p> <p>9 Q. Is that fair, the sequence I</p> <p>10 mentioned, in vitro to in vivo/animal to</p> <p>11 phase I, phase II, phase III, maybe phase IV?</p> <p>12 A. Yeah --</p> <p>13 MS. MILLER: Objection.</p> <p>14 THE WITNESS: -- I just wanted</p> <p>15 to understand --</p> <p>16 MS. MILLER: Dr. Boyd, please</p> <p>17 give me time to object.</p> <p>18 THE WITNESS: I just wanted to</p> <p>19 wrap my head around the massive</p> <p>20 context which -- we were talking about</p> <p>21 carcinogenicity, and now we're talking</p> <p>22 about therapeutic.</p> <p>23 So understanding that there's</p> <p>24 been a massive context switch in terms</p> <p>25 of the question that you're asking,</p>
<p style="text-align: right;">Page 287</p> <p>1 QUESTIONS BY MR. RESTAINO:</p> <p>2 Q. Doctor, isn't it true that in</p> <p>3 scientific research it's not uncommon,</p> <p>4 especially when looking at treatment</p> <p>5 modalities, to go from an in vitro cellular</p> <p>6 petri dish study, and if the results are</p> <p>7 promising, to move on to an in vivo study or</p> <p>8 an animal study, and if the results are</p> <p>9 promising, to move on to a phase I clinical</p> <p>10 trial, phase II, phase III, and in some cases</p> <p>11 phase IV?</p> <p>12 MS. MILLER: Objection.</p> <p>13 QUESTIONS BY MR. RESTAINO:</p> <p>14 Q. Would you agree that's normal</p> <p>15 sequence of some scientific study?</p> <p>16 MS. MILLER: Objection to those</p> <p>17 questions.</p> <p>18 THE WITNESS: To what kind of</p> <p>19 scientific study? Are we talking</p> <p>20 about treatment studies or toxicology,</p> <p>21 carcinogenicity studies?</p> <p>22 QUESTIONS BY MR. RESTAINO:</p> <p>23 Q. I actually started by saying,</p> <p>24 when looking at treatment study modalities,</p> <p>25 treatment study. Let's use a treatment</p>	<p style="text-align: right;">Page 289</p> <p>1 could you please ask the question</p> <p>2 again?</p> <p>3 QUESTIONS BY MR. RESTAINO:</p> <p>4 Q. You really need for me to</p> <p>5 repeat that, what normal study is for looking</p> <p>6 at the treatment modalities for any drug?</p> <p>7 In vitro goes on to in vivo,</p> <p>8 which might include animal, which might</p> <p>9 include phase I where you look at safety,</p> <p>10 phase II where we look at safety and dose,</p> <p>11 phase III where we're looking at effect,</p> <p>12 phase IV we're looking at -- for the</p> <p>13 production or any adverse events.</p> <p>14 Do you really need that</p> <p>15 repeated again?</p> <p>16 MS. MILLER: Objection.</p> <p>17 Is that your question?</p> <p>18 THE WITNESS: I'm --</p> <p>19 MS. MILLER: I would like to</p> <p>20 object to your tone, and if your</p> <p>21 question is "do you really need that</p> <p>22 repeated again," I'm going to object</p> <p>23 as argumentative.</p> <p>24 THE WITNESS: I actually didn't</p> <p>25 hear a word you said because you sound</p>

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<p style="text-align: right;">Page 290</p> <p>1 extremely angry and you're yelling at 2 me, and I frankly don't appreciate it. 3 QUESTIONS BY MR. RESTAINO: 4 Q. You're a scientist, correct? 5 Is that what you do for a 6 living? 7 A. Actually, I spend most of my 8 time as an administrator and as an executive 9 at this point in my career. 10 Q. What percentage of your time 11 today is spent in administrative versus 12 research? 13 A. 90 percent. 14 Q. Okay. Have you ever been 15 involved in testing for a potential treatment 16 of any condition? 17 A. That's an extraordinarily vague 18 question. 19 In what context? 20 Q. Let's say a drug treatment for 21 ovarian cancer. 22 Have you ever been involved 23 in -- in the experiment looking at whether a 24 particular compound could be an effective 25 treatment of ovarian cancer? Ever been</p>	<p style="text-align: right;">Page 292</p> <p>1 A. I agree that preclinical 2 studies are generally required for novel 3 compounds to get to a human phase I, 4 phase II, phase III and so forth studies, 5 yes. 6 Q. Would you criticize any 7 researcher who was conducting an in vitro 8 study, who at the same time was also not 9 testing that compound in an animal model at 10 the same time? 11 A. I would if that investigator 12 titled a paper, based on those in vitro 13 studies in a tissue culture dish, "Molecular 14 basis supporting the association of talcum 15 powder use with increased risk of ovarian 16 cancer." He's a long way from ovarian 17 cancer, sir. 18 Q. Okay. You can agree the next 19 step for any type of study like that -- but 20 now we're back to cancer, because you've made 21 a monumental change. We're back to the risk. 22 Would you agree that the next 23 step is in vivo? 24 A. No. I disagree that I've made 25 a monumental change. We've always been on</p>
<p style="text-align: right;">Page 291</p> <p>1 involved with that? 2 A. Are you done? 3 Q. Yes, sir. 4 A. Well, as I mentioned earlier, I 5 served on the committee for experimental 6 medicine of the gynecologic oncology group 7 for 17 years, and so I would offer to you 8 that it's a fair statement that I haven't 9 been -- I have been involved in the design of 10 studies, the purpose of which was to develop 11 clinical trials in ovarian cancer. 12 Q. And when you've been involved 13 in the design of these trials, or of these 14 studies, at what level? The in vitro level, 15 the in vivo or animal level, phase I, 16 phase II, phase III or all of them? 17 A. All of them. 18 Q. Is it your understanding then 19 in that -- in that situation that the normal 20 sequence is to go in vitro, and if the 21 results are positive, to move on to in vivo, 22 which might be animal, and then to move on to 23 phase I to phase II, phase III, maybe 24 phase IV? 25 Is that the normal sequence?</p>	<p style="text-align: right;">Page 293</p> <p>1 cancer. 2 Q. But I switched to the treatment 3 thing, and you criticized that as being a 4 monumental change. 5 So we're back to now risk and 6 cancer. 7 A. We've always been on cancer. 8 Q. Okay. 9 A. You switched from 10 carcinogenicity to therapeutics in cancer. 11 We've never shifted off cancer. 12 Q. Well, by definition we just 13 did. So I've changed the channel back to 14 cancer. 15 A. I disagree. 16 Q. Now looking in the cancer risk 17 area, is it normal science to conduct an in 18 vitro study contemporaneously with an animal 19 study? 20 MS. MILLER: Objection. 21 THE WITNESS: I've never 22 performed such a contemporaneous 23 study, no. 24 QUESTIONS BY MR. RESTAINO: 25 Q. If you take a look at your</p>

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<p style="text-align: right;">Page 294</p> <p>1 expert report now at the bottom of page 8, 2 and you've got a section there on CA125 3 findings, correct? 4 A. Correct. 5 Q. CA125 stand for cancer antigen 6 125? 7 A. Yes. 8 Q. And the last sentence on 9 page 8, going on to the next page, you state, 10 "The FDA-approved use of measuring serum 11 CA-125 levels is in the context of a bio -- 12 quote, biomarker, end quote, to monitor 13 response to ovarian cancer treatment. 14 Reference 28," which is Saed report at 18, 15 along with citing Jelovac D and Armstrong, 16 correct? 17 A. Correct. 18 Q. Would you agree that CA125 is 19 the most extensively studied biomarker for 20 use in the early detection of ovarian cancer? 21 MS. MILLER: Objection. 22 THE WITNESS: It's the only 23 putative biomarker for ovarian cancer; 24 thus, it would by definition be the 25 most extensively studied.</p>	<p style="text-align: right;">Page 296</p> <p>1 A. I think we've established that. 2 Q. Have you ever published on 3 CA125 since your 2000 publication, current 4 understanding of the epidemiology, clinical 5 implications of BRCA1, BRCA2 mutations for 6 ovarian cancer? 7 A. Well, there are a lot of 8 questions there. I'm not sure what BRCA1 and 9 BRCA2 have to do -- oh, I see. I published a 10 paper on whether -- yeah, now I've got it. 11 Okay. So other than that paper 12 where I believe the hypothesis was that CA125 13 levels may differ in BRCA1 and BRCA2-linked 14 ovarian cancers from matched ovarian cancers 15 not associated with BRCA1 or 2 mutations -- I 16 think that's the paper you're referring to. 17 Q. Okay. 18 A. I have, in fact, coauthored a 19 paper related to CA125 insofar as I chaired a 20 conference at the Banbury Center at the Cold 21 Spring Harbor Laboratory, the purpose of 22 which was to bring multiple content experts 23 together and dissect the UKCTOCS clinical 24 trial, which, of course, involved -- well, I 25 can explain the trial to you, but I'll stop</p>
<p style="text-align: right;">Page 295</p> <p>1 QUESTIONS BY MR. RESTAINO: 2 Q. The next sentence you write, 3 "Although such measurements have also been 4 tested experimentally for decades in an 5 effort to detect ovarian cancer at an early 6 age, the specificity and sensitivity of serum 7 CA125 levels in this context are unacceptably 8 low, and the assay is neither useful nor 9 approved for this purpose. Reference 29." 10 Did I read that correctly? 11 A. No, you said "age" instead of 12 "stage," but I'll give you that mistake. 13 Q. And your reference 29 says, 14 "See above reference to UKCTOCS clinical 15 trial"; is that correct? 16 A. Yes, we refer to it as the 17 UKCTOCS trial. United Kingdom Collaborative 18 Trial of Ovarian Cancer Screening is what the 19 acronym stands for. 20 Q. Okay. 21 A. I hope you heard my answer. 22 Q. I did, and I'm reading it also. 23 Do you order CA125 blood tests? 24 A. No. I'm not an oncologist. 25 Q. Okay.</p>	<p style="text-align: right;">Page 297</p> <p>1 there. The answer is yes. 2 Q. Okay. Now, regarding the 3 sensitivity being unacceptably low and the 4 assay has been neither useful nor approved 5 for this purpose, approved by whom? 6 A. The FDA. 7 Q. And it's your expert opinion as 8 you sit here that CA125 has not been approved 9 for use with detecting ovarian cancer? 10 A. That's not what I said. 11 Would you like me to read what 12 I said? 13 Q. I think the report itself will 14 stand on itself. 15 A. Well, you misstated my report, 16 sir. 17 Q. Well, go ahead so the record is 18 clear, sir. 19 A. The FDA-approved use of 20 measuring CA125 levels is in the context of a 21 biomarker to monitor response to treatment 22 and, I might add, recurrence, where it is 23 extremely effective. 24 Q. Okay. 25 A. It's not effective in any way,</p>

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<p style="text-align: right;">Page 298</p> <p>1 shape or form in the early detection or</p> <p>2 diagnosis of ovarian cancer, the context in</p> <p>3 which it's not FDA approved.</p> <p>4 Q. So it's your opinion it's not</p> <p>5 effective in any way, shape or form in the</p> <p>6 early detection or diagnosis of ovarian</p> <p>7 cancer; is that correct?</p> <p>8 A. Yes.</p> <p>9 Q. Okay. And now you have a</p> <p>10 reference here, your reference 30 of</p> <p>11 Scholler N and Urban N, CA125 in ovarian</p> <p>12 cancer, correct? That's your reference 30?</p> <p>13 A. I do see the reference 30 at</p> <p>14 the bottom of the page. I'd like to look to</p> <p>15 see what I am referencing it for. "Increased</p> <p>16 serum CA125 levels have been reported in</p> <p>17 benign conditions such as..."</p> <p>18 My point here is that the</p> <p>19 reason it's not FDA approved for the early</p> <p>20 detection or diagnosis of ovarian cancer are</p> <p>21 multifactorial, one being the sensitivity and</p> <p>22 specificity for ovarian cancer is</p> <p>23 extraordinarily low because increased serum</p> <p>24 levels of CA125, as I write here in reference</p> <p>25 Scholler and Urban, have been reported in,</p>	<p style="text-align: right;">Page 300</p> <p>1 Nicole Urban. And you can see down at the</p> <p>2 bottom, this is published in 2015 -- or at</p> <p>3 the top, Gynecologic Oncology 2015.</p> <p>4 When you were preparing for</p> <p>5 your expert report and evaluating CA125, did</p> <p>6 you see this paper?</p> <p>7 A. I didn't need to see it because</p> <p>8 I was already aware of it.</p> <p>9 Q. Okay. And if you could turn to</p> <p>10 the second page, bottom paragraph of the left</p> <p>11 column?</p> <p>12 A. Yes. A review?</p> <p>13 Q. It's above materials and</p> <p>14 methods on the second page, left column, five</p> <p>15 lines up.</p> <p>16 A. One, two, three --</p> <p>17 Q. Starts with "CA125" on the</p> <p>18 right-hand side. "CA125 is a predictive."</p> <p>19 Do you see that?</p> <p>20 A. Yes.</p> <p>21 Q. "CA125 is a predictive marker</p> <p>22 for EOC that becomes increasingly sensitive</p> <p>23 with proximity to diagnosis, reference 16."</p> <p>24 Do you have any objective</p> <p>25 evidence to contradict Urban, et al., in 2015</p>
<p style="text-align: right;">Page 299</p> <p>1 and I quote, benign conditions such as</p> <p>2 endometriosis, pregnancy, ovulation, liver</p> <p>3 diseases, congestive heart disease and</p> <p>4 infectious diseases, and so forth and so on.</p> <p>5 The other reason, perhaps</p> <p>6 unstated, is that if we presume for the</p> <p>7 moment that epithelial ovarian cancer is one</p> <p>8 disease, which it's not, but if we -- for the</p> <p>9 purposes of early diagnosis of the cancer,</p> <p>10 which we -- cancers which we lump together as</p> <p>11 epithelial ovarian carcinoma, only</p> <p>12 approximately half of all patients at the</p> <p>13 time of diagnosis of epithelial ovarian</p> <p>14 carcinoma have an elevated serum CA125; hence</p> <p>15 its lack of utility in early detection as</p> <p>16 well as its lack of specificity.</p> <p>17 (Boyd Exhibit 21 marked for</p> <p>18 identification.)</p> <p>19 QUESTIONS BY MR. RESTAINO:</p> <p>20 Q. Okay. Well, let's look at a</p> <p>21 more current publication by Nicole Urban.</p> <p>22 You reference Scholler and</p> <p>23 Urban, 2007. Here's "Identifying</p> <p>24 postmenopausal women at elevated risk for</p> <p>25 epithelial ovarian cancer." Lead author is</p>	<p style="text-align: right;">Page 301</p> <p>1 when they say "CA125 is a predictive marker</p> <p>2 for EOC that becomes increasing sensitive</p> <p>3 with proximity to diagnosis"?</p> <p>4 A. I'm not aware that this is in</p> <p>5 fact the case, and, you know, I -- it's hard</p> <p>6 to understand the context without having read</p> <p>7 a paper entitled "Assessing Lead Time," "lead</p> <p>8 time" typically being associated with the</p> <p>9 term "bias."</p> <p>10 Q. You testified that you're aware</p> <p>11 of this paper, correct?</p> <p>12 A. Yes, I'm aware of this paper.</p> <p>13 Q. And you reference --</p> <p>14 A. Where you're pulling the</p> <p>15 sentence out of one of many sentences in the</p> <p>16 paper and asking me to opine on a particular</p> <p>17 sentence.</p> <p>18 Q. Yeah, many sentences which have</p> <p>19 absolutely nothing to do with specificity and</p> <p>20 sensitivity and early detection of ovarian</p> <p>21 cancer, I'll give you that. I'm trying to</p> <p>22 stay on point of what you said.</p> <p>23 Now, look at the final sentence</p> <p>24 of that paragraph there, and they say, "Both</p> <p>25 CA125 and HE4 show promise as risk and early</p>

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<p style="text-align: right;">Page 302</p> <p>1 detection markers," again with a number of</p> <p>2 references, 16 and then 20 through 23. Five</p> <p>3 references, correct?</p> <p>4 MS. MILLER: You read that</p> <p>5 wrong.</p> <p>6 QUESTIONS BY MR. RESTAINO:</p> <p>7 Q. I'll read it again.</p> <p>8 "Both CA125 and HE4 show</p> <p>9 promise as risk and early detection markers."</p> <p>10 Did I read that correctly?</p> <p>11 A. You did.</p> <p>12 Q. Okay. Now, near the end of the</p> <p>13 paragraph of CA125, page 9 of your report --</p> <p>14 so we're on page 9, that top paragraph. Six</p> <p>15 lines up on the right-hand side, you write,</p> <p>16 "Because increased CA -- CA/125" --</p> <p>17 Do you see that, sir?</p> <p>18 A. Yes.</p> <p>19 Q. -- "expression can reflect any</p> <p>20 number of causes, physiologic states, or</p> <p>21 conditions other than ovarian cancer, its use</p> <p>22 as a detection tool is highly disfavored and</p> <p>23 is considered ineffective from a clinical</p> <p>24 perspective."</p> <p>25 I've read that correctly?</p>	<p style="text-align: right;">Page 304</p> <p>1 another article. This one's titled "Role of</p> <p>2 CA125 in predicting ovarian cancer survival -</p> <p>3 a review of the epidemiological literature"</p> <p>4 by Gupta, et al., published 2009 in the</p> <p>5 Journal of Ovarian Research.</p> <p>6 And 2009 is after the 2007</p> <p>7 paper by Scholler and Urban which you</p> <p>8 referenced, correct, sir?</p> <p>9 A. I'll submit that whatever you</p> <p>10 said is correct.</p> <p>11 Q. Okay. And if you look on the</p> <p>12 left -- on the second page, left column, you</p> <p>13 have a heading "CA125 in ovarian cancer."</p> <p>14 Do you see that, sir?</p> <p>15 A. Yes.</p> <p>16 Q. And they state here, "The most</p> <p>17 widely used tumor marker in ovarian cancer,</p> <p>18 often considered the gold standard, is CA125,</p> <p>19 reference 19."</p> <p>20 Did I read that correctly?</p> <p>21 A. You did.</p> <p>22 Q. And the reference 19 is by</p> <p>23 Hogdall, E, titled "Cancer antigen 125 and</p> <p>24 prognosis."</p> <p>25 Did you see that?</p>
<p style="text-align: right;">Page 303</p> <p>1 A. You did.</p> <p>2 Q. And you have the professional</p> <p>3 ability to use CA125 from a clinical</p> <p>4 perspective?</p> <p>5 MS. MILLER: Objection.</p> <p>6 THE WITNESS: No.</p> <p>7 QUESTIONS BY MR. RESTAINO:</p> <p>8 Q. And do you -- and you don't</p> <p>9 have any references for that statement</p> <p>10 either, do you?</p> <p>11 A. It's just a follow-on to the</p> <p>12 entire paragraph above it where I've provided</p> <p>13 references.</p> <p>14 And furthermore, if you're</p> <p>15 attempting to equate that sentence you read</p> <p>16 in my expert report with a hypothetical</p> <p>17 statement about two biomarkers together</p> <p>18 showing promise, I think it's an inaccurate</p> <p>19 comparison.</p> <p>20 Q. Okay.</p> <p>21 A. Apples meet oranges.</p> <p>22 (Boyd Exhibit 22 marked for</p> <p>23 identification.)</p> <p>24 QUESTIONS BY MR. RESTAINO:</p> <p>25 Q. I've just marked as Exhibit 22</p>	<p style="text-align: right;">Page 305</p> <p>1 A. I did.</p> <p>2 Q. And that was published in 2008?</p> <p>3 A. Right.</p> <p>4 Q. Also after Scholler and Urban,</p> <p>5 correct?</p> <p>6 A. Right.</p> <p>7 Q. Would you agree that CA125 is</p> <p>8 the most widely tumor marker in ovarian</p> <p>9 cancer?</p> <p>10 A. It's the only tumor marker used</p> <p>11 in ovarian cancer in a clinical context;</p> <p>12 thus, it's the most widely used.</p> <p>13 Q. Okay. Which --</p> <p>14 MS. MILLER: Let him finish,</p> <p>15 please.</p> <p>16 Please finish your answer.</p> <p>17 THE WITNESS: You know, it's</p> <p>18 late. Perhaps we could get beyond</p> <p>19 rhetorical questions and get to more</p> <p>20 substantive questions related to CA125</p> <p>21 and the pathogenesis of ovarian</p> <p>22 cancer, which is what Dr. Saed is</p> <p>23 attempting to suggest based on his</p> <p>24 work.</p> <p>25</p>

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<p style="text-align: right;">Page 306</p> <p>1 QUESTIONS BY MR. RESTAINO:  2 Q. Okay.  3 A. This all has to do, as you can  4 see from the title on relevance, the  5 relevance -- the possible relevance of CA125  6 in predicting the survival. It has nothing  7 to do with the tumorigenesis.  8 Q. Does it have anything to do  9 with tumor progression?  10 A. It has to do with survival from  11 advanced ovarian cancer.  12 Q. Okay. If you look at the same  13 paragraph we were just looking at in the  14 Gupta study, page 2, left column, all the way  15 down at the bottom, second to last -- four  16 lines up, they write, "In addition, elevated  17 levels of CA125 are more strongly associated  18 with serous, rather than mucinous, tumors,"  19 with reference 25.  20 Did I read that correctly?  21 A. You did.  22 Q. Okay. And do you agree with  23 that statement?  24 A. I would probably just say "so  25 what" with respect to Dr. Saed's work and his</p>	<p style="text-align: right;">Page 308</p> <p>1 autoantibodies, open paren, AAb, close paren,  2 that may have diagnostic capacity for  3 invasive epithelial ovarian cancer, with AABs  4 to p53 proteins and cancer-tested antigens,  5 open paren, CTAGs, as prominent examples."  6 Did I read that correctly?  7 A. You did.  8 Q. Okay. And on the third page in  9 the left column, at the bottom they have  10 materials and case methods.  11 Do you see that, sir?  12 A. Yes, I do.  13 And I have to respectfully  14 suggest that after we get through reading  15 sentences throughout this paper, that I'm  16 probably going to have ask you to -- to form  17 a coherent question related to all of these  18 comments that you're currently reading and  19 asking me if you're reading them correctly  20 throughout the paper.  21 Q. Okay. If you look at the  22 materials and methods, you see that this is  23 a -- we conducted a case-control study nested  24 within the EPIC cohort, hyphen, in a  25 population-based, multi-center prospective</p>
<p style="text-align: right;">Page 307</p> <p>1 suggestion that CA125 is somehow involved in  2 the transformation of a normal ovarian  3 epithelial cell into a malignant one.  4 (Boyd Exhibit 23 marked for  5 identification.)  6 QUESTIONS BY MR. RESTAINO:  7 Q. Okay. I'd like to show you now  8 a paper I've marked as Exhibit 23 by lead  9 author Kaaks, K-a-a-k-s, et al. And this is  10 titled "Tumor-associated autoantibodies as  11 early detection markers for ovarian cancer,  12 question mark, a prospective evaluation."  13 And this was published in the  14 International Journal of Cancer in 2018; is  15 that correct?  16 A. Let's assume you are correct.  17 I'll stipulate, yes.  18 Q. And if you look at the final  19 author line on the left, do you see there's  20 Daniel W. Cramer again, correct?  21 A. Correct.  22 Q. First sentence of the abstract,  23 which is on -- actually on page 2, they  24 write, "Immune-proteomic screening has  25 identified several tumor-associated</p>	<p style="text-align: right;">Page 309</p> <p>1 cohort study in ten European countries,  2 hyphen, further extension of an earlier study  3 on CA125 and other early detection markers  4 for ovarian cancer." Two references, 4 and  5 5.  6 Did I read that correctly?  7 A. You did.  8 Q. If you go back to the second  9 page where we have the abstract, et al., they  10 have a section there, What's New?  11 Do you see that, sir?  12 A. I do.  13 Q. And -- you know, I'm not going  14 to ask that because you've answered that  15 already, so let's strike that. I'll move on.  16 And you've mentioned the UK  17 Collaborative Trial of Ovarian Cancer  18 Screening, UKCTOCS?  19 Did you pronounce that acronym?  20 A. UKCTOCS is how we refer to it,  21 yes.  22 Q. UKCTOCS?  23 A. Uh-huh.  24 Q. Can I use that also?  25 A. Sure.</p>

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<p style="text-align: right;">Page 310</p> <p>1 (Boyd Exhibit 24 marked for 2 identification.) 3 QUESTIONS BY MR. RESTAINO: 4 Q. And I've marked that study as 5 Boyd 24. 6 And if you turn to this study 7 on the summary on page 2, background. 8 "Ovarian cancer has a poor prognosis, with 9 just 40 percent of patients surviving five 10 years. We designed this trial to establish 11 the effect of early detection by screening on 12 ovarian cancer mortality." 13 So a priori, they sought to 14 establish the effect of early detection by 15 screening on ovarian cancer mortality, 16 correct? 17 A. That was a horrible sentence. 18 I'm sorry. 19 Q. It wasn't -- 20 A. The purpose -- go ahead. 21 Q. It wasn't an ad hoc, after the 22 study was done. Let's take a look at it. 23 This was -- they set out to 24 look, right from the get-go, the effect of 25 early detection of screening on ovarian</p>	<p style="text-align: right;">Page 312</p> <p>1 Do you see that? 2 A. Yes. 3 Q. "The poor prognosis for ovarian 4 cancer, reference 1, motivated us to start a 5 program of screening research 30 years ago, 6 reference 2. We have since reported CA125 as 7 a predictor of ovarian cancer risk, reference 8 3 and 4, high specificity, reference 2, and 9 preliminary evidence of survival benefit, 10 reference 5, of multimodal screening using 11 CA125 interpreted with a cutoff with 12 transvaginal ultrasound as a second-line 13 test, development of a risk of ovarian cancer 14 algorithm, ROCA, for interpretation of 15 longitudinal CA125, reference 6 and 7. Use 16 of morphological criteria and second-line 17 vaginal ultrasound, reference 8, and use of 18 ROCA in a pilot, randomized controlled trial, 19 reference 9." 20 A. And you did a great job of 21 reading Dr. Ian Skates' summary of what I 22 just described to you prior to your having 23 read the summary of this clinical trial. 24 Q. Anywhere in this study do they 25 talk about the low specificity of using</p>
<p style="text-align: right;">Page 311</p> <p>1 cancer mortality? 2 A. Using a fairly complicated 3 algorithm known as ROCA -- 4 Q. Uh-huh. 5 A. -- with or without subsequent 6 TV, transvaginal, ultrasound in women based 7 on the ROCA algorithm, risk of ovarian 8 cancer, in women whose serum CA125 levels 9 rose in a consistent fashion. 10 So if you'd like me to explain 11 the clinical trial to you, I'd be happy to. 12 Q. No. 13 A. It was the largest prospective, 14 randomized clinical trial ever conducted in 15 the history of medicine, as far as I know. 16 It's very important. 17 Q. Well, let's take a look -- 18 well, if it's that important, your -- counsel 19 for Johnson &amp; Johnson can address it with 20 you. 21 I want you to look at the 22 introduction at page 3 of 31 of the study, 23 and there they write, "The poor prognosis for 24 ovarian" -- I'm sorry, sir, it's page 3 of 25 31. Introduction.</p>	<p style="text-align: right;">Page 313</p> <p>1 CA125? 2 A. Well, it's important to take 3 the verbiage in this paper in context. Ian 4 Jacobs, God bless him, spent, as he 5 indicates, 30 years of his life attempting to 6 develop the CA125 marker in one or another 7 context, in this case the ROCA algorithm, 8 followed by TVU, as an early detection marker 9 for ovarian cancer in order to reduce 10 morbidity and mortality from ovarian cancer. 11 And over the years, over the 12 30 years -- again, I have great respect for 13 Ian, as well as Steven Skates, the last 14 author who developed the ROCA algorithm, as 15 scientists and clinicians. I actually worked 16 with Ian back in the day when he was doing 17 some research in Durham. 18 And over the years, they 19 published many studies showing relatively 20 high specificity and sensitivity and accuracy 21 and so forth, which led them to launch this 22 monumental 200,000-woman clinical trial over 23 a 14-year period, which failed to show that 24 CA125, using the ROCA algorithm in 25 combination with TVU, was an effective early</p>

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<p>1 detection marker for ovarian cancer, using</p> <p>2 survival from ovarian cancer as the primary</p> <p>3 end point.</p> <p>4 And it was sad for all of us,</p> <p>5 but that's the reality of the study and the</p> <p>6 fate of CA125 as we sit here today as an</p> <p>7 effective marker for the early detection of</p> <p>8 ovarian cancer.</p> <p>9 (Boyd Exhibit 25 marked for</p> <p>10 identification.)</p> <p>11 QUESTIONS BY MR. RESTAINO:</p> <p>12 Q. Let's take a look one more in</p> <p>13 this area before we move on. Another paper</p> <p>14 titled "Early Detection of Ovarian Cancer,"</p> <p>15 which I've marked as 25, by Elias.</p> <p>16 Have you seen this paper</p> <p>17 before, sir?</p> <p>18 A. Probably. I try to read most</p> <p>19 things Bob Bast writes.</p> <p>20 Q. And you see this was published</p> <p>21 in Hematology and Oncological Clinics of</p> <p>22 North America last year, 2018, correct?</p> <p>23 A. Yes.</p> <p>24 Q. And if you look at the key</p> <p>25 points, first key point on the first page is,</p>	<p>1 Q. They've got a section there</p> <p>2 titled "Protein Biomarkers." And there,</p> <p>3 writing in 2018, they write, "CA125 remains</p> <p>4 the most sensitive and specific protein</p> <p>5 biomarker for detecting early stage disease</p> <p>6 in apparently healthy populations."</p> <p>7 Did I read that correctly?</p> <p>8 A. You did.</p> <p>9 Q. And that's in conflict to what</p> <p>10 you write in your expert report; is that</p> <p>11 correct?</p> <p>12 A. Where are we reading from my</p> <p>13 expert report?</p> <p>14 I'll only add with respect to</p> <p>15 the sentence that you read that for the fifth</p> <p>16 or sixth time, CA125 is the only known</p> <p>17 biomarker for epithelial ovarian cancer, so,</p> <p>18 thus, it's arguably the most effective, which</p> <p>19 is not very.</p> <p>20 Q. Okay. So --</p> <p>21 A. I'm happy to answer the second</p> <p>22 part related to my expert report, if you'd</p> <p>23 like to point out the sentence that --</p> <p>24 Q. Do you disagree that CA125</p> <p>25 remains the most sensitive and specific</p>
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<p>1 "Given the low prevalence of ovarian cancer</p> <p>2 even among postmenopausal women, 1 to 2,500,</p> <p>3 an effective screening strategy requires high</p> <p>4 sensitivity, open paren, greater than</p> <p>5 75 percent, close paren, and extremely high</p> <p>6 specificity, open paren, 99.7 percent, close</p> <p>7 paren."</p> <p>8 Did I read that correctly?</p> <p>9 A. I'll assume you did.</p> <p>10 Q. And they discuss the high</p> <p>11 specificity of CA125 in the previous study,</p> <p>12 the large clinical trial we discussed,</p> <p>13 correct?</p> <p>14 A. No, they did not.</p> <p>15 Q. They didn't --</p> <p>16 A. They said, in fact, that an</p> <p>17 effective screening strategy requires high</p> <p>18 sensitivity and extremely high specificity.</p> <p>19 Q. Okay.</p> <p>20 A. They made no reference to</p> <p>21 having achieved 99.7 percent specificity in</p> <p>22 any context.</p> <p>23 Q. Let's go to page 906 of the</p> <p>24 Elias study.</p> <p>25 A. Okay.</p>	<p>1 protein biomarker for detecting early stage</p> <p>2 disease in apparently healthy populations?</p> <p>3 MS. MILLER: Objection. Asked</p> <p>4 and answered. Multiple times.</p> <p>5 THE WITNESS: Is it okay to</p> <p>6 agree with defense counsel?</p> <p>7 MS. MILLER: No.</p> <p>8 MR. RESTAINO: Yes.</p> <p>9 MS. MILLER: Then they'll</p> <p>10 accuse me of coaching. Please don't</p> <p>11 do that.</p> <p>12 THE WITNESS: Oh, I see.</p> <p>13 I'm sorry, what was the</p> <p>14 question?</p> <p>15 QUESTIONS BY MR. RESTAINO:</p> <p>16 Q. Do you agree that CA125 in 2018</p> <p>17 remains the most sensitive and specific</p> <p>18 protein biomarker for detecting early stage</p> <p>19 disease in apparently healthy populations?</p> <p>20 MS. MILLER: Objection.</p> <p>21 THE WITNESS: And for the</p> <p>22 seventh time, yes, because it's the</p> <p>23 only biomarker for ovarian cancer.</p> <p>24 Thus, by definition, it would have to</p> <p>25 be the most sensitive, specific and</p>

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<p style="text-align: right;">Page 318</p> <p>1 effective, even though it's not</p> <p>2 effective in reducing mortality from</p> <p>3 ovarian cancer, as evidenced by the</p> <p>4 largest randomized, prospective,</p> <p>5 controlled clinical trial ever</p> <p>6 conducted in the history of medicine.</p> <p>7 QUESTIONS BY MR. RESTAINO:</p> <p>8 Q. Reducing mortality is an</p> <p>9 entirely different end point than early</p> <p>10 detection; isn't it correct?</p> <p>11 A. Well, what's the point of early</p> <p>12 detection if you're not going to reduce</p> <p>13 mortality?</p> <p>14 Q. Two different studies. Would</p> <p>15 you agree a study for -- that has a primary</p> <p>16 end point of early detection is entirely</p> <p>17 different from a study whose primary end</p> <p>18 point is decreased mortality?</p> <p>19 MS. MILLER: Objection.</p> <p>20 THE WITNESS: If such</p> <p>21 hypothetical studies existed, I would</p> <p>22 agree that the end points that you</p> <p>23 are -- that you articulated are indeed</p> <p>24 different end points.</p> <p>25 I personally, given the amount</p>	<p style="text-align: right;">Page 320</p> <p>1 cell line studies alone and the increase in</p> <p>2 CA125, while intriguing, are not sufficiently</p> <p>3 convincing."</p> <p>4 Did I read that correctly?</p> <p>5 A. You did.</p> <p>6 Q. Now, do you agree that the</p> <p>7 manuscript was well-written?</p> <p>8 A. No. It was horribly written.</p> <p>9 Q. Okay.</p> <p>10 A. It was impossible to follow, in</p> <p>11 fact, in my opinion.</p> <p>12 Q. Do you agree that the</p> <p>13 conclusions were supported by the results?</p> <p>14 A. No.</p> <p>15 Q. Do you agree that this is an</p> <p>16 important but controversial topic?</p> <p>17 A. What's the topic?</p> <p>18 Q. Regarding inflammation -- talc,</p> <p>19 inflammation and ovarian cancer.</p> <p>20 A. Hard to say.</p> <p>21 Q. Regarding this --</p> <p>22 MS. MILLER: Are you done with</p> <p>23 your answer? You sounded like you</p> <p>24 were continuing.</p> <p>25 THE WITNESS: I'm done.</p>
<p style="text-align: right;">Page 319</p> <p>1 of work that's gone into the study of</p> <p>2 CA125 as a predictive marker for the</p> <p>3 early detection of ovarian cancer,</p> <p>4 would suggest that the only reason for</p> <p>5 having pursued those studies over</p> <p>6 30 years would have been to reduce</p> <p>7 mortality from ovarian cancer. And</p> <p>8 I'll stop there.</p> <p>9 QUESTIONS BY MR. RESTAINO:</p> <p>10 Q. Okay. Let's turn to page 9 of</p> <p>11 your expert report, the last paragraph, and</p> <p>12 then we'll take a break.</p> <p>13 A. Thank you.</p> <p>14 Q. You're welcome.</p> <p>15 Are you there, sir?</p> <p>16 A. Last paragraph on page 9?</p> <p>17 Q. Page 9.</p> <p>18 "These opinions are generally</p> <p>19 shared by reviewer number 1, who provided a</p> <p>20 critique of Dr. Saed's manuscript following</p> <p>21 submission to Gynecologic Oncology. The</p> <p>22 reviewer writes that, quote, the significance</p> <p>23 of the study would be greatly enhanced if a</p> <p>24 mouse model corroborated the cell line</p> <p>25 findings. In this reviewer's opinion, the</p>	<p style="text-align: right;">Page 321</p> <p>1 Please.</p> <p>2 QUESTIONS BY MR. RESTAINO:</p> <p>3 Q. Would you agree the</p> <p>4 significance of the study would be enhanced</p> <p>5 if a mouse model corroborated the cell line</p> <p>6 findings?</p> <p>7 A. With respect to what?</p> <p>8 Q. The significance of the study.</p> <p>9 A. Well --</p> <p>10 MS. MILLER: Do you want to</p> <p>11 show us where you're reading from?</p> <p>12 THE WITNESS: He's reading, I</p> <p>13 think, the reviewer comments.</p> <p>14 MS. MILLER: Do you want to go</p> <p>15 back to that exhibit?</p> <p>16 THE WITNESS: Yeah, perhaps I</p> <p>17 should.</p> <p>18 I thought we were done, I'm</p> <p>19 sorry, with that particular document.</p> <p>20 MS. MILLER: Do you remember</p> <p>21 what number it is?</p> <p>22 Do you want me to go through</p> <p>23 the file and pull it?</p> <p>24 MS. EMMEL: It is Exhibit 19, I</p> <p>25 believe.</p>

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<p>1 THE WITNESS: Did we go through</p> <p>2 them in order? So in other words,</p> <p>3 I'll find Exhibit 19 before 20?</p> <p>4 MS. MILLER: Theoretically.</p> <p>5 THE WITNESS: Yes, here it is.</p> <p>6 QUESTIONS BY MR. RESTAINO:</p> <p>7 Q. And I was reading from, whether</p> <p>8 it's paragraph number 1 or bullet point</p> <p>9 number 1, one of the reviewers that states</p> <p>10 the significance of this study.</p> <p>11 A. Yes, and I'm, for the record,</p> <p>12 correlating my remarks in my expert report</p> <p>13 with the location in the Gynecologic Oncology</p> <p>14 review document. And I'm simply quoting the</p> <p>15 reviewer to some extent, hence the quotation</p> <p>16 marks.</p> <p>17 Q. Okay. So I'm asking? When the</p> <p>18 reviewer says, "The significance of the study</p> <p>19 would be greatly enhanced if a mouse model</p> <p>20 corroborated the cell line findings," do you</p> <p>21 agree?</p> <p>22 A. No, I believe the study has no</p> <p>23 inherent significance.</p> <p>24 Q. Okay.</p> <p>25 A. As presented. And so</p>	<p>1 A. Yes.</p> <p>2 Q. SNPs, for the court reporter.</p> <p>3 -- "identified by the Dr. Saed</p> <p>4 in his background discussion of ovarian</p> <p>5 cancer-associated polymorphisms was observed</p> <p>6 in his talc study."</p> <p>7 Did I read that correctly?</p> <p>8 A. Yes.</p> <p>9 Q. Did any of the peer reviewers</p> <p>10 bring out that observation?</p> <p>11 A. I think there was one comment</p> <p>12 by the peer reviewers on the whole genotype</p> <p>13 switching mess.</p> <p>14 Reviewer 1 stated in his or her</p> <p>15 second comment: "The significance of SNP</p> <p>16 alterations should be further clarified."</p> <p>17 Q. And that is something that can</p> <p>18 be done with a subsequent experiment,</p> <p>19 correct?</p> <p>20 A. No, I honestly think that he or</p> <p>21 she was referring to the -- had the same</p> <p>22 response that I did inasmuch as the data were</p> <p>23 just indescribably confusing in terms of</p> <p>24 hypothesis and conclusion.</p> <p>25 Q. Where does any of those words</p>
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<p>1 reproducing insignificant, tortured,</p> <p>2 illogical findings in a mouse model would not</p> <p>3 increase the veracity of the data presented</p> <p>4 in the paper published in Reproductive</p> <p>5 Biology -- I'm sorry, I can't remember the</p> <p>6 journal in which it ultimately appeared.</p> <p>7 MR. RESTAINO: Okay. Why don't</p> <p>8 we go ahead and take a break at this</p> <p>9 point.</p> <p>10 VIDEOGRAPHER: Off the record</p> <p>11 at 4:08 p.m.</p> <p>12 (Off the record at 4:08 p.m.)</p> <p>13 VIDEOGRAPHER: We're back on</p> <p>14 the record at 4:21 p.m.</p> <p>15 QUESTIONS BY MR. RESTAINO:</p> <p>16 Q. Doctor, as we wind down to the</p> <p>17 11 -- proverbial eleventh hour, will you turn</p> <p>18 to page 12 of your expert report? And the</p> <p>19 first full paragraph starts off with a</p> <p>20 bolded, italicized "second."</p> <p>21 Do you see that, sir?</p> <p>22 A. I do.</p> <p>23 Q. "Second, none of the SNP" --</p> <p>24 A. SNPs.</p> <p>25 Q. I can say "snips"?</p>	<p>1 appear in the peer reviewer's notes?</p> <p>2 A. They don't. I'm making -- I'm</p> <p>3 making an inference.</p> <p>4 Q. Okay.</p> <p>5 A. By what I'm reading.</p> <p>6 Q. Now --</p> <p>7 A. If I had received this review,</p> <p>8 that would say to me that I need to explain</p> <p>9 better what the heck it was I was trying to</p> <p>10 show in my paper, not that I needed to do</p> <p>11 more experiments.</p> <p>12 Q. Can reasonable scientists</p> <p>13 disagree with your interpretation of that</p> <p>14 review and proceed differently?</p> <p>15 A. Sure. It's getting late.</p> <p>16 Q. In the middle of the paragraph,</p> <p>17 you have -- you discuss a meta-analysis of 43</p> <p>18 case-control studies.</p> <p>19 Do you see that, sir?</p> <p>20 A. Yes.</p> <p>21 Q. A meta-analysis of 43</p> <p>22 case-control studies involving various types</p> <p>23 of cancer found no association between the RS</p> <p>24 2333227 polymorphism, open paren, MPO, close</p> <p>25 paren, and an increased cancer risk."</p>

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<p style="text-align: right;">Page 326</p> <p>1 Did I read that correctly?</p> <p>2 A. You did.</p> <p>3 Q. And what was the purpose of you</p> <p>4 including that meta-analysis in your report?</p> <p>5 A. You know, this is a very long</p> <p>6 and dense section written two months ago, and</p> <p>7 furthermore, the reason it's very long and</p> <p>8 dense is because I was doing my best to</p> <p>9 interpret an incredibly dense series of</p> <p>10 experiments and point out why in my mind they</p> <p>11 were flawed.</p> <p>12 So to be honest with you, I</p> <p>13 just simply can't take a sentence out of</p> <p>14 four-page commentary on the SNP experiments</p> <p>15 and do this deposition justice. I'm sorry.</p> <p>16 Q. Did you review your expert</p> <p>17 report in preparation --</p> <p>18 A. Of course I did.</p> <p>19 (Boyd Exhibit 26 marked for</p> <p>20 identification.)</p> <p>21 QUESTIONS BY MR. RESTAINO:</p> <p>22 Q. Okay. I've now marked as an</p> <p>23 exhibit the Chu, et al., meta-analysis titled</p> <p>24 "The MPO -463 G, greater than symbol, A</p> <p>25 polymorphism and cancer risk: A</p>	<p style="text-align: right;">Page 328</p> <p>1 there.</p> <p>2 So, first of all, it would seem</p> <p>3 that the authors of this paper on this</p> <p>4 particular polymorphic variant are opining on</p> <p>5 the free radicals exceeding antioxidant</p> <p>6 defense mechanisms, generally speaking, in</p> <p>7 cancer development, not in ovarian cancer</p> <p>8 specifically.</p> <p>9 And then the title of the paper</p> <p>10 referenced is "Oxidative stress inactivates</p> <p>11 the human DNA mismatch repair system," so I'm</p> <p>12 not really sure how DNA mismatch repair,</p> <p>13 which is one of four major mechanisms of DNA</p> <p>14 repair in mammals, is relevant to this whole</p> <p>15 sentence preceding the reference.</p> <p>16 Q. Okay. This is a peer-reviewed,</p> <p>17 published paper in Mutagenesis, correct?</p> <p>18 A. Correct, but my answer stands.</p> <p>19 Q. And this is a reference in your</p> <p>20 expert report, correct?</p> <p>21 A. The Mutagenesis paper.</p> <p>22 Q. Yes.</p> <p>23 A. Question mark.</p> <p>24 Q. Okay. Now, the right column of</p> <p>25 the first page, last full paragraph</p>
<p style="text-align: right;">Page 327</p> <p>1 meta-analysis based on 43 case-control</p> <p>2 studies," Mutagenesis.</p> <p>3 Did I read that correctly?</p> <p>4 A. Yes.</p> <p>5 Q. If you look at the first page,</p> <p>6 the left column, Introduction, they start off</p> <p>7 by saying, "Cancer is a multifactorial</p> <p>8 disease that results from complex</p> <p>9 interactions between the environmental and</p> <p>10 genetic factors."</p> <p>11 Did I read that correctly?</p> <p>12 A. You did.</p> <p>13 Q. And we discussed that earlier</p> <p>14 today, correct?</p> <p>15 A. Many times.</p> <p>16 Q. Yes.</p> <p>17 And then the next sentence is</p> <p>18 that "Evidence suggests that oxidative</p> <p>19 stress, defined as a state where the levels</p> <p>20 of free radicals exceed antioxidant defense</p> <p>21 mechanism, plays a crucial role in cancer</p> <p>22 development," reference number 2.</p> <p>23 Did I read that correctly?</p> <p>24 A. Yes, you did, so let's look at</p> <p>25 reference number 2 and then take it from</p>	<p style="text-align: right;">Page 329</p> <p>1 between -- before materials and methods.</p> <p>2 If you see that, you look up,</p> <p>3 they start off the final sentence saying,</p> <p>4 "Considering the extensive role of NPO in the</p> <p>5 carcinogenic process, we performed a</p> <p>6 meta-analysis of all eligible case-control</p> <p>7 studies to estimate the overall cancer risk</p> <p>8 of this polymorphism and to quantify the</p> <p>9 potential between studied heterogeneity."</p> <p>10 Did I read that correctly?</p> <p>11 A. Yes, you did.</p> <p>12 Q. Would you agree that</p> <p>13 heterogeneity is an inherent limitation in</p> <p>14 meta-analyses?</p> <p>15 A. I'm sorry, I'm just trying to</p> <p>16 keep up. Could you restate the question?</p> <p>17 Q. Would you agree that the</p> <p>18 concept of heterogeneity is an inherent</p> <p>19 limitation in meta-analyses?</p> <p>20 A. I have a two-pronged answer.</p> <p>21 Actually, it's only one.</p> <p>22 My simple answer is this: I'm</p> <p>23 not an expert in epidemiologic studies, and I</p> <p>24 have no -- I can't answer the question.</p> <p>25 Q. Okay. In this study, I think</p>

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<p style="text-align: right;">Page 330</p> <p>1 you reference -- if you look at page 391, 2 there's a Table 1. And if you look at the 43 3 studies here making up this meta-analysis, 4 can you share with the Court how many studies 5 from this meta-analysis which you are relying 6 upon for your expert opinion in this matter 7 involve ovarian cancer? 8 MS. MILLER: Objection. 9 THE WITNESS: One, question 10 mark? 11 QUESTIONS BY MR. RESTAINO: 12 Q. The Olson 2004 study? 13 A. Sorry, I've got to find it 14 again. The Olson 2004 appears to say 15 "ovarian cancer," yes, with 122 cases and 396 16 controls. 17 Q. And if you just scroll through 18 the cancer type column, just roughly 19 speaking, would you agree that most of the -- 20 of the studies involved lung cancer? 21 A. That's a fair statement. 22 Q. Would you agree that there are 23 different genetic components and risk factors 24 associated with lung cancer as there is with 25 ovarian cancer?</p>	<p style="text-align: right;">Page 332</p> <p>1 Please repeat your current 2 question. 3 MS. MILLER: Wait. Wait. 4 Do you need to clean up your 5 last answer or explain -- or what are 6 you saying? 7 THE WITNESS: No. Apparently I 8 was citing this paper, Chu, et al., 9 and I'm willing to let it go at this 10 point. 11 QUESTIONS BY MR. RESTAINO: 12 Q. Okay. The question that I 13 asked now, Doctor, is, did you find any, as 14 you described them, invariably smudged 15 handwritten page numbers which contributed in 16 your opinion to the overall results of the 17 study? 18 MS. MILLER: Objection. 19 THE WITNESS: Well, again, with 20 all due respect, sir, that's a bizarre 21 question. 22 I -- looking through that 23 particular notebook, I found that 24 every single page number had either 25 been, in my opinion, whited out and</p>
<p style="text-align: right;">Page 331</p> <p>1 A. I'm sorry, could you repeat the 2 question? 3 Q. Would you agree that there are 4 different genetic components and risk factors 5 associated with lung cancer as compared to 6 ovarian cancer? 7 A. Yes. 8 Q. Do you understand the concept 9 of external validity as it relates to 10 epidemiological studies? 11 A. I'm not going to comment on 12 epidemiologic studies, and especially 13 methodology underlying epidemiologic studies. 14 That's not my area of expertise. 15 Q. Okay. Doctor, did you find any 16 invariably smudged handwritten page numbers 17 which substantively affected the results of 18 the study? 19 A. I'm sorry, I got sidetracked, 20 but we've gone past the question. 21 The polymorphism as I described 22 it in my expert report was based on its 23 description in the human genome, whereas this 24 paper was looking -- it's a retrospective 25 comment.</p>	<p style="text-align: right;">Page 333</p> <p>1 written over or erased and written 2 over, which, in my mind, generally 3 speaking, calls into question the 4 validity of every shred of data on 5 every one of those pages, and when it 6 was performed and how it was 7 performed, and so on and so forth. 8 One simply does not change 9 every page number in a laboratory 10 notebook. 11 QUESTIONS BY MR. RESTAINO: 12 Q. Your expert report on page 23, 13 the top paragraph, the very first full 14 paragraph -- and I'll wait for you to get 15 there. I'm sorry. 16 A. It's all right. 17 Q. You write, "Regardless, if one 18 considers the data table in question, the 19 first horizontal row concludes on the far 20 right with a, quote, average, end quote, 21 value of 11.07 for three replicative values 22 of 9.98, 11.63, and 10.50, reference 99. The 23 correct average would have been 10.70." 24 Did I read that correctly, sir? 25 A. Yes.</p>

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<p>1 Q. Is that data in the final 2 published manuscript? 3 A. No, he doesn't publish the raw 4 data in the final manuscript. 5 Q. And in any of the graphs in the 6 final manuscript, are the graphs specific 7 enough to show what that difference in 8 average would show? 9 A. That's a great question, and 10 the answer is no. It's impossible to discern 11 from the histograms in the final paper which 12 numbers the histograms actually represent. 13 Absolutely impossible. 14 One can at best come up with a 15 rough estimate based on the Y axis of what 16 the histograms represent. 17 Q. Regarding the Dr. Saed -- or 18 Fletcher, et al.'s, published paper 19 disclosure regarding the declaration of a 20 conflict of interest, it's your expert 21 opinion that the published conflict of 22 interest statement is inappropriate? Is that 23 correct? 24 A. Well, first, let's just be 25 clear. When I wrote my expert opinion, the</p>	<p>1 I can tell from the chain of events, the 2 version of the manuscript that was accepted 3 by the journal -- and I apologize, 4 Reproductive Sciences, but we're all familiar 5 with the name of the journal, I think -- did 6 not at that time have the declaration. 7 Q. Okay. 8 A. And so the reviewers, the two 9 or more individuals who would have judged, in 10 addition to the science, any potential 11 influence that a conflict of interest may 12 have had on the explication of the science, 13 they were unaware of that relationship, to 14 the extent that the relationship is 15 adequately defined. And that's the second 16 problem with the declaration. 17 So first, the reviewers didn't 18 see it when they accepted the paper. 19 Second, it's a completely 20 open-ended declaration of conflict. In other 21 words, if I were reviewing the paper and knew 22 that he was a paid consultant for plaintiffs 23 in the litigation, which of course his paper 24 supports, then that would very much factor 25 into my opinion as opposed to a paid</p>
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<p>1 only manuscript I had available to review had 2 no acknowledgements or declarations of 3 conflicting interests. And so naturally I 4 would write an expert report that found that 5 to be completely unacceptable under the 6 circumstances. 7 Q. Is your opinion different today 8 based upon the published article itself? 9 A. Not in a substantial way, and 10 I'll tell you why. 11 First, while I would like to 12 think he took my critique to heart and 13 decided to include a declaration of 14 conflicting interests in the ultimate 15 published version of the paper where he says 16 some other stuff about -- in his preface, the 17 gist of the declaration is that Dr. Saed has 18 served as a paid consultant, an expert 19 witness, in the talcum powder litigation. 20 Q. Okay. 21 A. And in my mind, there are two 22 major problems with this declaration. 23 First, as memory serves -- and 24 I received multiple copies of the manuscript 25 over time from defense attorneys. As far as</p>	<p>1 consultant for defense representing Johnson &amp; 2 Johnson. 3 Q. That wouldn't factor into your 4 opinion? 5 A. No, it certainly would. I'm 6 just simply stating it's a binary. 7 Q. Okay. 8 A. So in other words, you're 9 either a paid consultant, an expert witness, 10 for plaintiffs or for defense. 11 Q. Okay. Is it -- 12 A. And he doesn't specify. And so 13 it's a meaningless declaration of conflict. 14 Q. Okay. Is it your opinion that 15 a scientist is likely to bias his 16 experimental results in a way that favors 17 whoever funded him or her? 18 A. I'm not going to comment on 19 individuals and their motives. I'm going to 20 comment on how I interpret this completely 21 meaningless declaration of conflicting 22 interests. 23 Q. Okay. 24 A. It was not present when the 25 paper was accepted and is meaningless after</p>

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<p style="text-align: right;">Page 338</p> <p>1 he added it in terms of which side he was 2 serving as an expert witness on. 3 Q. Are you a biased witness 4 inasmuch as you're being paid \$1,200 an hour 5 by Johnson &amp; Johnson? 6 A. No. 7 Q. Do you have any reason to 8 believe any of the plaintiff experts are 9 biased because they're being paid by the 10 plaintiffs? 11 A. Actually, it's my impression 12 that plaintiffs, based on Dr. Saed's 13 deposition transcript, funded -- well, it's 14 very murky. 15 Q. And I'm sorry, sir, I was just 16 referring to the other plaintiff experts who 17 have performed -- who written expert reports 18 like yourself. 19 Are they biased because 20 plaintiff attorneys are paying them? 21 MS. MILLER: He's trying to 22 answer a question, and you interrupted 23 him. 24 THE WITNESS: I believe that 25 it's quite possible that Dr. Saed was</p>	<p style="text-align: right;">Page 340</p> <p>1 cancer. 2 I would agree with my statement 3 if -- and if it's an accurate reflection of 4 your question, then the answer is yes. 5 Q. I would adopt that, sir. 6 If prevention strategies are to 7 be developed, would you agree that 8 sophisticated markers for risks are needed, 9 such as SNPs, epidemiology and lifestyle? 10 MS. MILLER: Objection. 11 THE WITNESS: Well, that's a 12 very bad sentence. I'm sorry, sir. 13 QUESTIONS BY MR. RESTAINO: 14 Q. Oh, Okay. 15 A. Epidemiology is not a marker, 16 for example. 17 Q. Okay. March 2007, did you 18 attend a conference in Lake Como, Italy? 19 A. I certainly attended a 20 conference in Lake Como, Italy. It was 21 beautiful. I can't honestly say when it was. 22 Q. To refresh your memory, does it 23 sound like the 11th ovarian cancer 24 action/HHMT forum, Lake Como -- 25 A. Helene Harris Memorial Trust,</p>
<p style="text-align: right;">Page 339</p> <p>1 biased based on the fact he was being 2 paid to write this paper. 3 QUESTIONS BY MR. RESTAINO: 4 Q. I'm sorry? 5 A. With respect to other 6 plaintiffs' expert witnesses, obviously I 7 have no reason to think that they would have 8 been biased. 9 Q. Do you agree that the 10 identification of women at an increased risk 11 for ovarian cancer will facilitate the 12 prevention and early detection in some 13 patients? 14 A. I'm sorry -- 15 MS. MILLER: Objection. 16 THE WITNESS: Please repeat. 17 QUESTIONS BY MR. RESTAINO: 18 Q. Do you agree that the 19 identification of women at increased risk for 20 ovarian cancer will facilitate prevention and 21 early detection in some patients? 22 A. So if I can restate, the 23 identification of women at increased risk for 24 ovarian cancer could potentially result in 25 primary or secondary prevention of said</p>	<p style="text-align: right;">Page 341</p> <p>1 yes, that rings a bell. 2 Q. Next question. 3 That meeting is held every four 4 years; is that correct? 5 A. Used to be. I think it's 6 petered out over the years, but -- 7 unfortunately. But at that time, I think it 8 was actually held every two years, 9 alternating between Europe and the United 10 States. 11 But go ahead, please. 12 Q. Were you a delegate at the 13 meeting? 14 A. At that particular meeting? 15 Q. Yes. 16 MS. MILLER: 12 years ago? 17 MR. RESTAINO: Yes. 18 THE WITNESS: In 2007? 19 QUESTIONS BY MR. RESTAINO: 20 Q. Yes. 21 A. If by "delegate" you mean was I 22 a participant, yes. 23 Q. Okay. As you sit here today, 24 do you recall if Dan Cramer was a delegate at 25 the meeting?</p>



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<p style="text-align: right;">Page 342</p> <p>1 A. I can't recall, but I'm 2 guessing he probably was or you wouldn't have 3 asked the question. 4 Q. Do you know -- 5 MS. MILLER: Please don't 6 speculate, sir. 7 THE WITNESS: Okay. Thank you. 8 QUESTIONS BY MR. RESTAINO: 9 Q. Do you know if Dr. Roberta Ness 10 was a delegate at the meeting? 11 A. No. 12 Q. And do you recall if one goal 13 of the meeting was the determination of women 14 at risk for ovarian cancer? 15 A. My memory is that most of the 16 HHMT ovarian cancer symposia or scientific 17 conferences were extremely broad in scope, 18 and I don't remember ever attending one -- I 19 only attended several -- where there was 20 special attention paid to any given topic 21 related to ovarian cancer. 22 Q. So -- 23 A. Typically it was -- again, to 24 use the term I used before, it spanned the 25 waterfront, if you will.</p>	<p style="text-align: right;">Page 344</p> <p>1 Do you recall an algorithm 2 being developed at that conference in 2007 3 which used seven risk factors, including age 4 over 45, family history of ovarian cancer, 5 early onset breast cancer, Jewish ethnicity, 6 no oral contraceptive use, no live births, no 7 breastfeeding, no tubal ligation, and 8 long-term genital talc usage? 9 Do you recall that, sir? 10 MS. MILLER: Objection. 11 THE WITNESS: Well, I'm sorry 12 to have allowed you to burn through 13 some of your important time, but as I 14 said before, the only thing I remember 15 about that meeting 12 years ago was 16 the scenery. 17 QUESTIONS BY MR. RESTAINO: 18 Q. Okay. Do you recall a 19 conference report coming out of that meeting 20 12 years ago? 21 A. Not specifically. My memory of 22 the HHMT meetings is they typically led to 23 some type of meeting summary that usually got 24 published somewhere. 25 (Boyd Exhibit 27 marked for</p>
<p style="text-align: right;">Page 343</p> <p>1 Q. So do you recall if at the 2 meeting a discussion was had regarding a 3 combination of demographic, reproductive and 4 environmental risk factors might be used to 5 develop a model that would more accurately 6 predict risk? 7 MS. MILLER: Objection. 8 THE WITNESS: In all 9 seriousness, sir, the only thing I 10 remember about the meeting is the 11 scenery. 12 QUESTIONS BY MR. RESTAINO: 13 Q. Do you remember developing -- 14 any algorithm being developed at that 15 conference which looked at seven risk factors 16 for ovarian cancer -- 17 MS. MILLER: Objection. Sorry. 18 I thought you were done. 19 QUESTIONS BY MR. RESTAINO: 20 Q. -- including age over 45? 21 MS. MILLER: Objection. Asked 22 and answered. 23 QUESTIONS BY MR. RESTAINO: 24 Q. This is going to be a long 25 question. Give me a second. Okay.</p>	<p style="text-align: right;">Page 345</p> <p>1 identification.) 2 QUESTIONS BY MR. RESTAINO: 3 Q. I've marked as our last exhibit 4 a paper titled "Opportunities and challenges 5 in ovarian cancer research, a perspective 6 from the 11th Ovarian cancer action-HHMT 7 Forum, Lake Como, March 2007." 8 And if you would turn to the 9 last page. 10 A. Sorry, I'm just trying to get 11 rid of some stuff. 12 The reference page? 13 Q. The very last page is a list of 14 authors. 15 A. Yes. 16 Q. Do you see the sixth author 17 listed there? 18 A. I recognize the guy, yeah. 19 Q. Jeffrey A. Boyd, Anderson 20 Cancer Institute, Savannah, Georgia? 21 A. That's me. 22 Q. That's you? 23 A. That's me. 24 Q. Okay. Now, if we can turn to 25 the first page, sir, the right column, the</p>



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<p style="text-align: right;">Page 346</p> <p>1 second full paragraph, you and your coauthors  2 in 2007 wrote, "A combination of demographic,  3 reproductive and environmental risk factors  4 might be used to develop a model that would  5 more accurately predict risk. One  6 preliminary algorithm using seven risk  7 factors, open paren, age over 45; long-term  8 genital talc usage; family history of ovarian  9 cancer or early onset breast cancer; Jewish  10 ethnicity; no oral contraceptive, open paren,  11 OC, close paren, use; no live births; no  12 breastfeeding; no tubal ligation, close  13 paren, show that women with six to seven of  14 these events have an odds ratio of 7.59,  15 reference 3."  16 Did I read that correctly?  17 A. I'll submit that you did.  18 Q. Do you understand that OR, as  19 used in this paragraph, stands for an odds  20 ratio?  21 A. Yes.  22 Q. Is it also fair to say that  23 since 2007 you knew that an algorithm was  24 established which in 2008, as a coauthor, you  25 published that showed a woman with six to</p>	<p style="text-align: right;">Page 348</p> <p>1 existed.  2 I mean, you can pull out  3 sentences from my papers dating back  4 to perhaps 1980, when I may have  5 published my first, and suggest that I  6 remember every paragraph and every  7 paper, or perhaps, again, with due  8 respect, in a more sinister fashion,  9 suggested that I've ignored paragraphs  10 in over 200 papers, I think is just  11 simply unfair and disingenuous.  12 QUESTIONS BY MR. RESTAINO:  13 Q. Do you think it's unfair and  14 disingenuous in a litigation where you've  15 criticized plaintiff experts for the  16 biological plausibility of talc causing  17 ovarian cancer, when in 2007 you and your  18 other delegates developed an algorithm which  19 was published in 2008 showing that women with  20 six to seven of the risk factors you  21 established then had an odds ratio of 7.59  22 for developing ovarian cancer and you left  23 that out of your expert report?  24 MS. MILLER: Objection.  25 THE WITNESS: Well, first of</p>
<p style="text-align: right;">Page 347</p> <p>1 seven of the risk factors we've been  2 discussing all day, including long-term  3 genital talcum powder usage, had an odds  4 ratio of 7.59 for the development of ovarian  5 cancer?  6 MS. MILLER: Objection.  7 Misstates the paragraph that you're  8 basing it on.  9 THE WITNESS: If we could just  10 leave out the hypothesis, what's the  11 essence of your question? Without  12 rereading all of the algorithm,  13 please, sir.  14 QUESTIONS BY MR. RESTAINO:  15 Q. You have known since the  16 conference in 2007, in your publication in  17 2008, that an algorithm was developed using  18 six to seven risk factors as we've been  19 discussing all day, and showed that a woman  20 with six to seven of these events had an OR  21 of 7.59; is that correct?  22 MS. MILLER: Same objection.  23 THE WITNESS: I would suggest  24 that I haven't known since the day I  25 read this paper that these data</p>	<p style="text-align: right;">Page 349</p> <p>1 all, let's go back to your implication  2 that I was involved in the development  3 of the algorithm. I wasn't.  4 This was, as all meetings are,  5 a conglomeration of multiple content  6 experts in multiple areas.  7 My expertise is not in the  8 development of risk factor algorithms.  9 Other authors who signed this paper  10 undoubtedly developed that algorithm.  11 My role at this meeting was to  12 explain the state of the art in terms  13 of the genetic basis of ovarian  14 cancer, if I recall.  15 QUESTIONS BY MR. RESTAINO:  16 Q. You are the coauthor of a  17 paper, peer-reviewed and published in 2008,  18 or 11 years ago, which indicated that women  19 with six to seven of the risk factors we've  20 discussed all day have a 659 percent  21 increased risk of developing ovarian cancer,  22 are you not?  23 MS. MILLER: Objection. That's  24 a false statement. That's a --  25 there's seven objectionable things,</p>

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<p>1 but you don't want me to say that</p> <p>2 them, so objection with a capital</p> <p>3 o-b-g-e -- whatever you said.</p> <p>4 THE WITNESS: Sir, I honestly</p> <p>5 don't know what you're trying to get</p> <p>6 me to say, but I wasn't involved in</p> <p>7 the development of this algorithm.</p> <p>8 QUESTIONS BY MR. RESTAINO:</p> <p>9 Q. You were involved --</p> <p>10 A. Other meeting attendees were.</p> <p>11 This is not my expertise any more than some</p> <p>12 of the immunologists at this meeting had</p> <p>13 nothing to do with the sections of the paper</p> <p>14 dealing with genetic risk.</p> <p>15 Q. Instead of being listed as one</p> <p>16 of the many delegates, as listed at the back</p> <p>17 of this, you are listed as one of the</p> <p>18 coauthors of this paper --</p> <p>19 MS. MILLER: Objection.</p> <p>20 QUESTIONS BY MR. RESTAINO:</p> <p>21 Q. -- correct?</p> <p>22 MS. MILLER: Objection.</p> <p>23 That's --</p> <p>24 MS. SHARKO: Where?</p> <p>25 MS. MILLER: Where?</p>	<p>1 document.</p> <p>2 A. Which one?</p> <p>3 Q. The one we were just</p> <p>4 discussing.</p> <p>5 A. Okay.</p> <p>6 Q. Under Key Recommendations --</p> <p>7 A. Where are you?</p> <p>8 Q. On page 656.</p> <p>9 A. Yes, sorry, 656.</p> <p>10 Q. Do you see the key</p> <p>11 recommendations?</p> <p>12 A. Yes. I'm sorry, were you</p> <p>13 waiting for me? I'm sorry.</p> <p>14 Q. How many are there?</p> <p>15 A. One, two, three, four, five,</p> <p>16 six -- 12 or 13.</p> <p>17 Q. Was there any recommendation to</p> <p>18 suggest to women not to use talc perineally?</p> <p>19 A. No.</p> <p>20 MS. MILLER: I have nothing</p> <p>21 else.</p> <p>22 REDIRECT EXAMINATION</p> <p>23 QUESTIONS BY MR. RESTAINO:</p> <p>24 Q. In that same section, was there</p> <p>25 any recommendations regarding oral</p>
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<p>1 MS. SHARKO: Oh, here.</p> <p>2 QUESTIONS BY MR. RESTAINO:</p> <p>3 Q. We've established that that is</p> <p>4 you, correct, Doctor?</p> <p>5 A. Yes. It's my memory that in</p> <p>6 order to be listed as a coauthor, you needed</p> <p>7 to be an invited speaker, and that's the</p> <p>8 difference between the -- all the individuals</p> <p>9 listed here who attended the meeting out of</p> <p>10 some kind of scientific or medical interest</p> <p>11 versus myself, who was invited to opine on</p> <p>12 factors related to genetic risk for ovarian</p> <p>13 cancer; not to develop or to discuss a</p> <p>14 possible epidemiologic early detection</p> <p>15 algorithm.</p> <p>16 MR. RESTAINO: Okay. I have no</p> <p>17 further questions.</p> <p>18 THE WITNESS: I guess I have no</p> <p>19 further answers.</p> <p>20 CROSS-EXAMINATION</p> <p>21 QUESTIONS BY MS. MILLER:</p> <p>22 Q. Dr. Boyd, I have just have one</p> <p>23 more question for you.</p> <p>24 A. Okay.</p> <p>25 Q. I'm going back to this</p>	<p>1 contraceptive usage?</p> <p>2 And it's late, and I'm not</p> <p>3 going to play games with you.</p> <p>4 Just look at the fifth bullet</p> <p>5 point, sir.</p> <p>6 A. "Raise awareness of oral</p> <p>7 contraceptive use in high-risk women carries</p> <p>8 a BRCA and in women at conventional risk."</p> <p>9 Q. Okay. Did you agree with that</p> <p>10 statement at the time?</p> <p>11 A. Yes.</p> <p>12 Q. Okay. When did you first come</p> <p>13 to your opinions regarding the association of</p> <p>14 talc powder -- of talc and ovarian cancer?</p> <p>15 A. I think you asked this question</p> <p>16 at the beginning of the deposition, and I, if</p> <p>17 I recall, answered roughly over 30 years of</p> <p>18 passive absorption of the literature, to the</p> <p>19 extent I pay attention to the ovarian cancer</p> <p>20 literature -- and I do, on a daily basis --</p> <p>21 if such literature, in fact, existed 30 years</p> <p>22 ago, that's when.</p> <p>23 MR. RESTAINO: Okay. No</p> <p>24 further questions.</p> <p>25 MS. MILLER: Thanks.</p>

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<p style="text-align: right;">Page 354</p> <p>1 VIDEOGRAPHER: This concludes 2 today's deposition. The time is 3 4:58 p.m. 4 We're off the record. 5 (Deposition concluded at 4:58 p.m.) 6 ----- 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25</p>	<p style="text-align: right;">Page 356</p> <p>1 INSTRUCTIONS TO WITNESS 2 3 Please read your deposition over 4 carefully and make any necessary corrections. 5 You should state the reason in the 6 appropriate space on the errata sheet for any 7 corrections that are made. 8 After doing so, please sign the 9 errata sheet and date it. You are signing 10 same subject to the changes you have noted on 11 the errata sheet, which will be attached to 12 your deposition. 13 It is imperative that you return 14 the original errata sheet to the deposing 15 attorney within thirty (30) days of receipt 16 of the deposition transcript by you. If you 17 fail to do so, the deposition transcript may 18 be deemed to be accurate and may be used in 19 court. 20 21 22 23 24 25</p>
<p style="text-align: right;">Page 355</p> <p>1 CERTIFICATE 2 3 I, CARRIE A. CAMPBELL, Registered 4 Diplomate Reporter, Certified Realtime 5 Reporter and Certified Shorthand Reporter, do 6 hereby certify that prior to the commencement 7 of the examination, Jeffrey A. Boyd, Ph.D. 8 was duly sworn by me to testify to the truth, 9 the whole truth and nothing but the truth. 10 I DO FURTHER CERTIFY that the 11 foregoing is a verbatim transcript of the 12 testimony as taken stenographically by and 13 before me at the time, place and on the date 14 hereinbefore set forth, to the best of my 15 ability. 16 17 I DO FURTHER CERTIFY that I am 18 neither a relative nor employee nor attorney 19 nor counsel of any of the parties to this 20 action, and that I am neither a relative nor 21 employee of such attorney or counsel, and 22 that I am not financially interested in the 23 action. 24 25 CARRIE A. CAMPBELL, NCRA Registered Diplomate Reporter Certified Realtime Reporter Notary Public Dated: April 9, 2019</p>	<p style="text-align: right;">Page 357</p> <p>1 ACKNOWLEDGMENT OF DEPONENT 2 3 4 I, _____, do 5 hereby certify that I have read the foregoing 6 pages and that the same is a correct 7 transcription of the answers given by me to 8 the questions therein propounded, except for 9 the corrections or changes in form or 10 substance, if any, noted in the attached 11 Errata Sheet. 12 13 14 15 16 17 18 19 20 21 22 23 24 25</p> <p>Jeffrey A. Boyd, Ph.D. DATE _____</p> <p>Subscribed and sworn to before me this ____ day of _____, 20 ____.</p> <p>My commission expires: _____</p> <p>Notary Public</p>

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